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# Enantioselective synthesis and (bio)catalysis

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# ENANTIOSELECTIVE SYNTHESIS AND (BIO)CATALYSIS

*Routes to Enantiomerically Pure Alcohols and Thiols*

**Colofon**

**In de ban van de chiraliteit**

Voorkant: *Handtekening met ratje* door H.E. ter Haar

Achterkant: foto van de jonge auteur

This research was sponsored by The Netherlands Organization for Scientific Research (N.W.O.)

NWO

RIJKSUNIVERSITEIT GRONINGEN

# ENANTIOSELECTIVE SYNTHESIS AND (BIO)CATALYSIS

## Routes to Enantiomerically Pure Alcohols and Thiols

Proefschrift

ter verkrijging van het doctoraat in de
Wiskunde en Natuurwetenschappen
aan de Rijksuniversiteit Groningen
op gezag van de
Rector Magnificus Dr. F. van der Woude
in het openbaar te verdedigen op
vrijdag 3 november 1995
des namiddags te 4.00 uur

door

**Robert Patrick Hof**

geboren op 7 april 1968
te Groningen

Promotor: Prof. Dr. R.M. Kellogg

# Voorwoord

Na vier jaar onderzoek, en enige maanden schrijftijd, is dan eindelijk 'het boekje' af. Tijdens mijn onderzoek hebben diverse personen een essentiële bijdrage aan het geheel geleverd waarvoor ik allen van harte wil bedanken. Zonder jullie hulp had dit boekje er zeker heel anders uitgezien. Een aantal personen wil met name bedanken. Allereerst natuurlijk mijn promotor Prof. Dr. R.M. Kellogg. De vrijheid die ik heb gekregen om het onderzoek op mijn manier te verrichten heb ik altijd gewaardeerd. Hierdoor was ik in staat een geheel eigen (kronkelende) lijn aan het onderzoek te geven. Hoewel we wel eens twijfels hebben gehad over deze gevolgde lijn denk ik toch dat we allebei met tevredenheid en plezier op de afgelopen vier jaar terug kunnen kijken.

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Veel succes allemaal,

Robert

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## Samenvatting

# Chapter 1

# Introduction

## 1.1 General introduction

A unifying topic in this thesis is the development of routes to optically active compounds. The importance today of chiral -- optically pure -- compounds is evident. The phenomena of optical activity and chirality were discovered about one and a half century ago by pioneering work of Pasteur,[1] van 't Hoff[2] and Le Bel.[3] Once the impact of chiral compounds on living organisms was realized,[4] major efforts were undertaken to find effective routes to optically pure compounds. The best (or worst) known example in this respect is thalidomide (sold as Softenon), of which only one of the enantiomers proved to have the desired sedative effect, whereas the other enantiomer caused severe fetal damage.[5] This has had a major effect on developments in pharmaceutical, agrochemical, and flavour and fragance industry. Whereas only some years ago most synthetic drugs were sold as racemates, nowadays more and more are sold as single enantiomers.[6] Also FDA regulation on the marketing of new drugs has become much more strict in recent years with respect to chiral compounds.[7]

Nowadays, there are several well established routes to optically pure compounds (figure 1.1), of which three were followed during this research; these are highlighted in figure 1.1.

The first part of this thesis is dedicated to the synthesis of new chiral compounds (thiols) starting from naturally occuring enantiomerically pure compounds (the so-called chiral pool).[8] The products of these reactions have possible applications in catalysis and synthesis.

The second part deals with the use of these chiral molecules in asymmetric catalysis. Special attention has been devoted to this topic during the last decades. In catalytic asymmetric synthesis one starts with prochiral substrates and tries to induce chirality in the product by the use of a chiral (bio)catalyst. In the transition state there is an interaction between the reactants and the chiral catalyst. Therefore, diastereomeric transition states (with a different Gibbs energy) arise. The reaction path will proceed by preference *via* the lowest transition state forming one of the enantiomers in excess. If the energy gap, $\Delta\Delta G^{\ddagger}$, between the two diastereomeric transition states becomes $>3$ kcal/mol, one enantiomer is formed exclusively. The technique is especially elegant since by the action of a small amount of optically pure material manifold amounts of new optically active material can be prepared. Much research has been devoted to the topic of asymmetric catalysis during the last two decades and it has

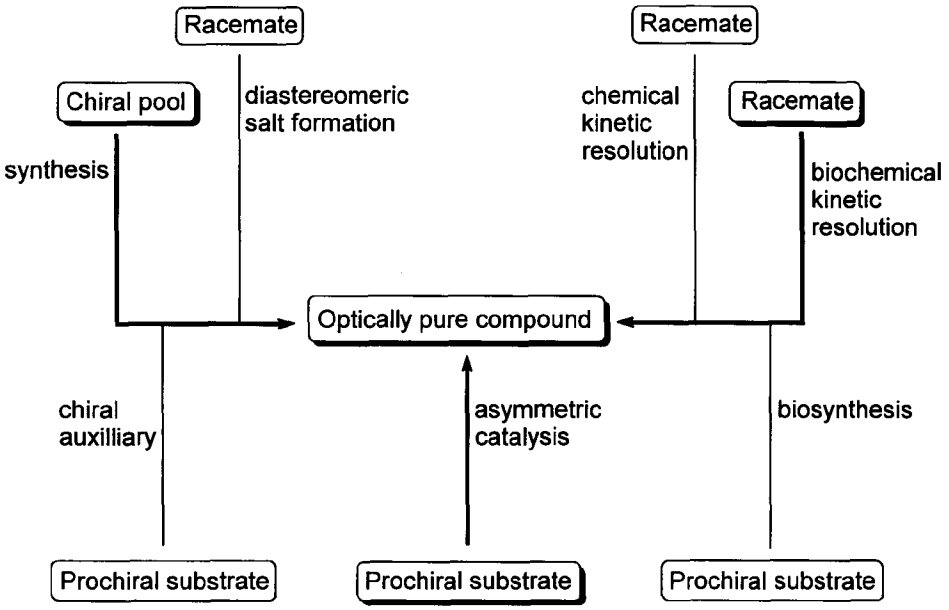


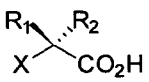

*Figure 1.1 Routes to optically pure compounds*

resulted in several successful examples. Only ten years ago the achievement of an e.e. in the product of 80% was considered to be a great success. Nowadays such results are commonplace and many reactions are known that proceed with an e.e. of >98%. In recent years, excellent books with many examples have appeared. The reader is referred to these for further information.[9]

The last two sections of the thesis deal with the use of enzymes for the resolution of racemates into the optical antipodes. The resolutions were carried out in organic media using a catalytic amount of enzyme. This is a technique which has become popular during the last decade.[10] The technique is based on the fact that enzymes will catalyze preferentially the reaction of one the enantiomers of a racemate into the product. After a certain period of time one enantiomer will have been converted completely to the product; the remaining substrate will therefore be optically pure. A major advantage is that always optically pure starting material can be obtained, if there is a difference in reaction rate for the enantiomers (see chapter 5, figure 5.1). A major drawback of the process is, however, that the maximum yield of an optically pure compound is only 50% as one starts with a one to one mixture of enantiomers. The yield can, however, sometimes be improved by racemization of the unwanted enantiomer. As the use of lipases in organic solvents is a new technique in our laboratories a special introductory chapter is devoted to the topic (chapter 5).

## 1.2 Aims of this thesis

One of the major research interests in our research group is asymmetric synthesis and catalysis. There is a special interest in the synthesis of optically pure analogs of simple biomolecules. For example, in the last decade several routes have been developed in our group to optically active α-alkylated α-hydroxy acids **1.1a**,[11] α-alkylated α-mercapto acids **1.1b**[12] and α-alkylated α-amino acids **1.1c**[13] which have, in contrast to their natural analogs, *two* alkyl substituents at the chiral center (figure 1.2).



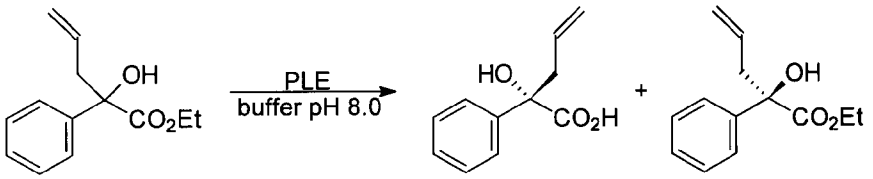

**1.1**

(or enantiomer)

**a** X = OH, $R_1$ = alkyl, $R_2$ = alkyl
**b** X = SH, $R_1$ = alkyl, $R_2$ = alkyl
**c** X = $NH_2$, $R_1$ = alkyl, $R_2$ = alkyl and $R_1$ is not $R_2$

*Figure 1.2 Tertiary α-hydroxy, mercapto and amino acids*

Another research topic, which was opened by Moorlag in cooperation with DSM, is the application of enzymes for the resolution of racemates.[11] In this way α-alkylated α-hydroxy acids were prepared in optically enriched form. Optically pure material could be obtained by subsequent recrystallization. The use of a biocatalyst proved to be far more successful than the use of chiral ligands for the preparation of these intermediates (scheme 1.1)




**1.1a**

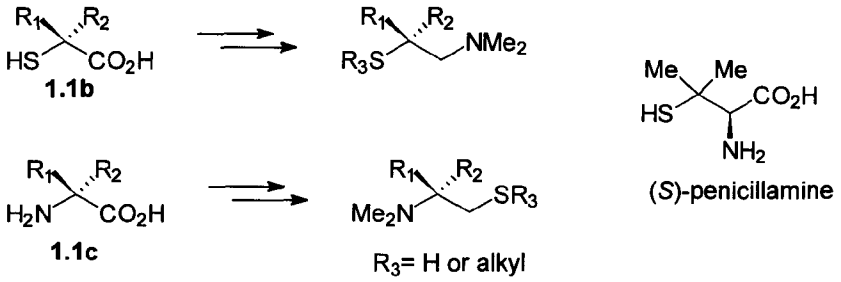
44% yield
83% e.e.

41% yield
86% e.e.

*Scheme 1.1 PLE catalyzed resolution of α-alkylated α-hydroxy acids by Moorlag*

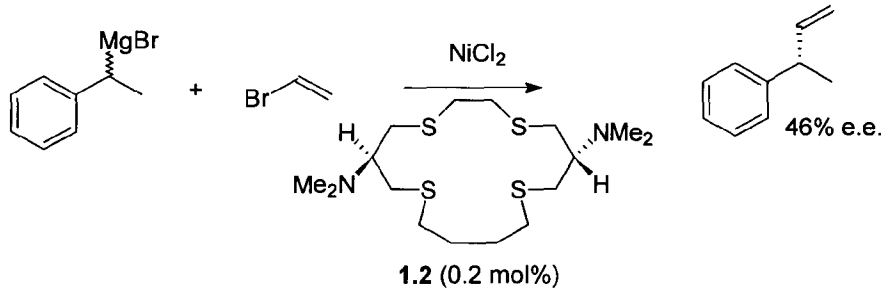
A well known research topic of our group is the use of cesium carbonate/DMF for the macrocyclization of thiocrown ethers.[14] Following this procedure even several chiral thiocrown ethers have been prepared.[15]
The aim of this study was to combine the research topics described above and to prepare optically active compounds, preferentially derived from the optically pure α-functionalized acids **1.1a-c**, which might be interesting in either transition metal catalysis or the synthesis of new chiral crown ethers.
Initially, we focussed on tertiary β-amino thiols and sulfides, derivatives of **1.1b**

and c, which might be interesting intermediates for transition metal catalysis as such compounds are known to have affinity for a wide variety of transition metals such as Zn(II),[16] Cu(II),[17] Co(II),[17,18] Ni(II),[17] Ni(0),[17] Pd(0),[17] Pt(0)[17] and Ga(III).[19] Also they show analogy to some pharmacologically active molecules such as penicillamine.[20] Routes to these amino thiols and sulfides starting from either **1.1b** or c are shown in scheme 1.2.




*Scheme 1.2 β-amino thiols and sulfides derived from **1.1b** and **c***

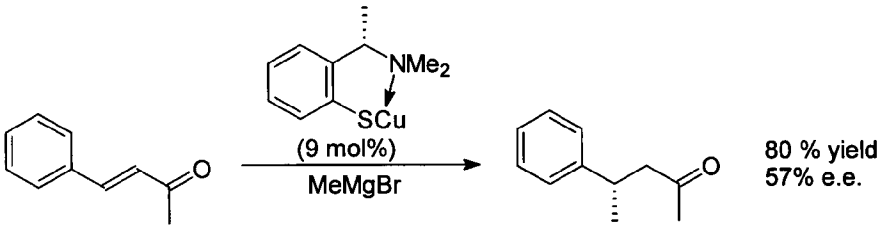
Previous to this research, amino thiols and sulfides had been used as ligands in Co(I),[21] Rh(I),[22] Cu(I)[23] and Ni(0)[24] catalyzed asymmetric transformations, although the enantiomeric excesses obtained are only moderate. For example, in our group, Vriesema showed that macrocylic amino sulfide ligand **1.2** catalyzed the cross-coupling reaction of vinyl bromide with a Grignard reagent in the presence of $NiCl_2$ with 46% e.e. (scheme 1.3).[24] An application of this reaction is the preparation of the analgestic Ibuprofen in optically active form.[25]




*Scheme 1.3 Asymmetric cross-coupling catalyzed by a chiral amino sulfide crown ether*

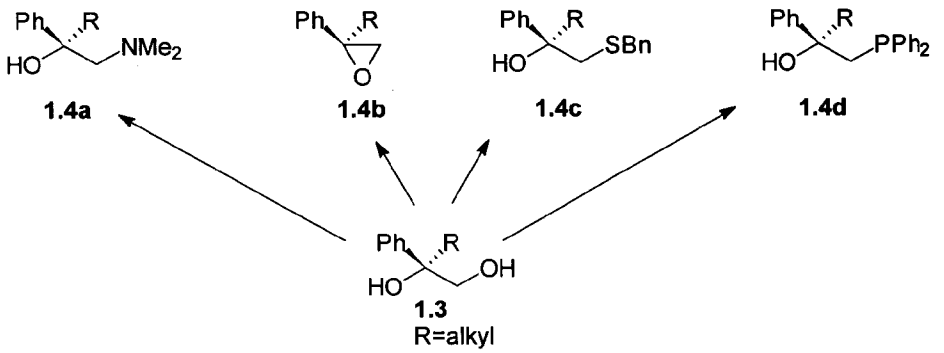
Another interesting result was obtained by van Koten in the copper thiolate catalyzed conjugate addition of Grignard reagents to enones, which gave the product in up to 57% e.e. (scheme 1.4).[23]
In analogy to β-amino alcohols, β-amino thiols might also be suitable ligands for

the asymmetric 1,2-addition of diethylzinc to aldehydes. A range of β-amino alcohols are known to give high enantiomeric excesses in this reaction.[26] The use of β-amino thiols and β-amino sulfides in this reaction was, however, not known prior to our research.
Also for the synthesis of new chiral thio or azacrown ethers, amino thiols and sulfides might be valuable intermediates.




*Scheme 1.4 Copper thiolate catalyzed conjugate Grignard addition by van Koten*

Encouraged by the results of Moorlag,[11] we decided to continue to investigate the possibilities of applying enzymes for the resolution of tertiary substrates. Substrates could be α-mercapto acids like **1.1b**, but also diols **1.3** might be interesting. Such diols are readilly available in optically pure form by reduction of α-hydroxy acids **1.1a**. These tertiary glycols have been applied in the synthesis of active fungicides and the activity of these agrochemicals was shown to be dependent on the absolute configuration.[27] The route followed has, however, some drawbacks such as the price of some of the reagents. Also, glycols **1.3** are interesting intermediates for the synthesis of new tertiary ligands and building blocks such as amino alcohols **1.4a**, epoxides **1.4b**, hydroxy sulfides **1.4c** and hydroxy phosphines **1.4d** (scheme 1.5).




*Scheme 1.5 Glycol **1.3** as building block for optically pure tertiary substrates*

Moreover, **1.3** could be applied in the synthesis of chiral sterically crowded crown ethers. Some of these transformations had already been shown in the literature to be possible for racemic analogs.[28]

### 1.3 Contents of this thesis

The first two chapters of this thesis deal with the synthesis of optically pure thiols. In chapter 2 attempts are outlined to convert optically pure tertiary $\alpha$-mercapto acids **1.1b** to the corresponding tertiary $\beta$-amino thiols. An important building block for **1.1b** is optically pure thiolactic acid. In chapter 2 a new and economical route to this compound (and its enantiomer) is described making use of the biocatalyst Pig liver esterase (PLE).[29] Also the application of (*R*)-thiolactic acid in the preparation of valuable thiazolidinones is decribed. In chapter 3 another class of optically pure $\beta$-amino thiols and sulfides is presented. These are derived from the optically pure ephedra alkaloids ephedrine and pseudo-ephedrine *via* ring opening of aziridines by sulfur nucleophiles.[30] In this way a variety of new optically pure $\beta$-amino thiols and sulfides was prepared. Results of the $\beta$-amino thiols described in chapters 2 and 3 in transition metal catalyzed transformations are described in chapter 4.[31] For reasons of simplicity, we chose the 1,2 addition of diethylzinc to benzaldehyde as a reaction to test the scope of our new ligands. As chapters 6 and 7 deal with the application of enzymes in organic solvents (a new research topic in these laboratories) a brief introduction dealing with this subject is presented in chapter 5. Chapter 6 deals with the lipase catalyzed resolution of tertiary diols of type **1.3**. Indeed, we were able to prepare optically pure diols **1.3** *via* lipase catalyzed resolution.[32] Some remarkable effects with respect to selectivity and chiral recognition were observed. From the obtained results an active site model for a specific lipase was postulated which, sofar, seems to have predictive value. Finally, in the last chapter results are described for the resolution of another class of racemic tertiary substrates. Also in this case good chiral recognitions were observed. The, in enantiomerically pure form, obtained compounds are not only known as building blocks for active fungicides, but might be suitable for the preparation of tertiary aryloxypropanolamines as well. Such compounds show a strong resemblance to known $\beta$-blockers,[20] and might therefore be of pharmaceutical interest.

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# Chapter 2

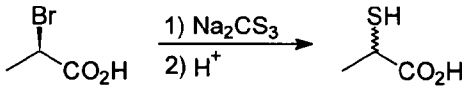
# (*R*)-Thiolactic acid as building block for chiral non-racemic β-amino thiols

## 2.1 Introduction

One of the most abundant types of chiral ligands used in asymmetric catalysis are β-amino alcohols. Both natural (such as ephedra or cinchona alkaloids) and synthetic molecules of this class have been used with great success in, for example, transition metal catalyzed transformations.[1] The use of the corresponding β-amino thiols, however, so far is limited. One of the major barriers for the application of these molecules is the lack of simple synthetic transformations to these interesting molecules. Previously in our group, synthetic procedures had been developed to produce enantiomerically pure thiols. In principle these thiols can be converted to enantiomerically pure β-amino thiols. However, since chiral secondary thiols can be prone to racemization under certain conditions, we made, initially, the extra proviso that the chiral center in our target molecules had to be tertiary. Since we had already gained experience with α-alkylation of α-mercapto acids to tertiary α-mercapto acids *without* racemization,[2] we tried to combine these two aspects in the synthesis of tertiary β-amino thiols.

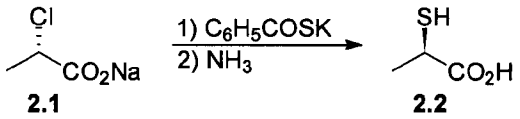
## 2.2 Synthesis of chiral thiols

The classical way to prepare thiols is the reaction between a sulfur nucleophile and an alkyl halide, tosylate or another compound having a good leaving group. Most often, direct substitution of an halide or tosylate by a hydrosulfide ($HS^-$) is only partially successful due to sulfide and disulfide formation. Therefore, usually other (protected) sulfur nucleophiles are used, which give, after deprotection, the free thiol. To prepare optically pure thiols this way one has to start from an optically pure halide or tosylate which has to be substituted by a sulfur nucleophile with complete inversion (pure $S_N2$) or complete retention. Usually this technique works fairly well unless an electron withdrawing group is adjacent to the chiral center. The presence of a thiol and an electron withdrawing group on a chiral center makes the α-proton more acidic, which can lead to substantial racemization under the general (alkaline) reaction conditions.
Due to this phenomenon the synthesis of optically pure α-mercapto acids, such as thiolactic acid, is a problem. For example, substitution of optically active α-bromo carboxylic acids with trithiocarbonate gives, after deprotection, partially racemized α-mercapto acids (scheme 2.1).[3]
Also substitution under Mitsunobu conditions was shown not to be completely




*Scheme 2.1 Synthesis of partially racemized thiolactic acid by the action of trithiocarbonate on α-bromopropanoic acid*

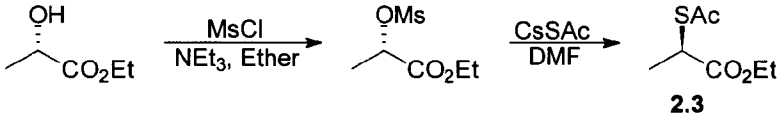
stereospecific.[4] This problem was first solved by Owen and Rahman, who were able to prepare (*R*)-thiolactic acid (**2.2**) by substitution of the sodium salt of (*S*)-2-chloropropanoic acid (**2.1**) with potassium thiobenzoate in boiling acetone followed by subsequent deprotection with ammonia (scheme 2.2).[5]




**2.1** **2.2**

*Scheme 2.2 Synthesis of optically pure thiolactic acid by Owen and Rahman*

The reaction conditions for this type of substitution had, however, to be controlled very carefully to prevent racemization.
Previous work in our group had already shown that the cesium salt of a carboxylic acid in DMF could substitute optically pure mesylates and halides in a pure $S_N2$ reaction.[6] This combination of reagent and solvent was extended in our group by Strijtveen for the synthesis of chiral thiols.[7] It was shown that cesium salts of thiolacetic acid and thiobenzoic acid (prepared *in situ* from the thiol acid and cesium carbonate) could substitute optically active halides and mesylates, having an adjacent electron withdrawing group, with little or no racemization in DMF. An example is the substitution of the mesylate of (*S*)-ethyl lactate, which gives the thiol acetate **2.3** in high yield in optically pure form (scheme 2.3).



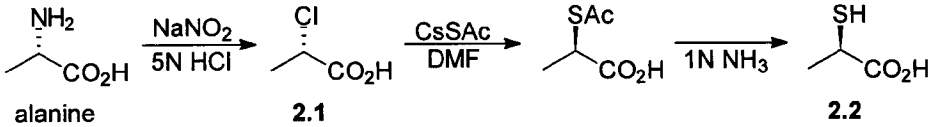

**2.3**

*Scheme 2.3 Synthesis of optically pure thiolacetate derived from ethyl lactate*

## 2.3 Synthesis of (*R*)-thiolactic acid

As mentioned in the foregoing section, the mesylate of (*S*)-ethyl lactate can be substituted to give ethyl (*R*)-(acetylthio)lactate (**2.3**) with complete inversion of configuration. However, during hydrolysis of the ethyl ester to the free α-mercapto

*acid* substantial racemization always takes place.[7] This problem was circumvented previously by Strijtveen via direct substitution of optically pure (*S*)-2-chloropropanoic acid (**2.1**),[7] prepared with retention of configuration from the amino acid alanine, with cesium thioacetate in DMF, followed by deprotection with ammonia (scheme 2.4).



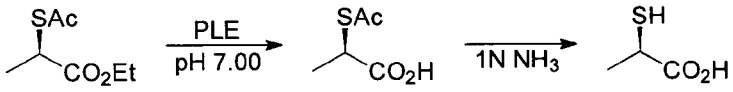

alanine **2.1** **2.2**

*Scheme 2.4 Synthesis of (R)-thiolactic acid from alanine*

The total yield of **2.2** based on the rather expensive alanine, however, never exceeds 35%. Especially, since the interest in both enantiomers of thiolactic acid has increased substantially in recent years, it would be very attractive if we could find a more economical route to prepare both (*R*)-and (*S*)-thiolactic acid from a common cheap starting material such as (*S*)-ethyl lactate. For example, **2.2** has been used in the synthesis of new Platelet Activating Factor (PAF) receptor antagonists,[8] and it was found that the activity was dependent on the absolute configuration.[9] Also active antiulcer agents have been derived form optically pure **2.2**,[10] and **2.2** has been used as an analog of Ala-82 in the backbone of T4 lysozyme.[11]

## 2.4 Synthesis of (*R*) and (*S*)-thiolactic acid from (*S*)-ethyl lactate[12]

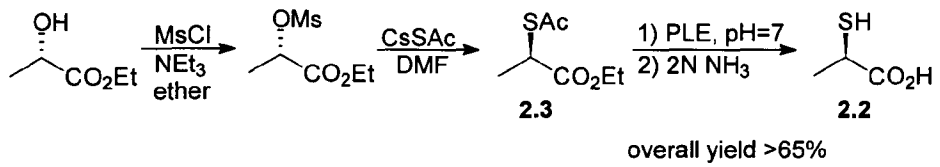
As we had had some good experiences using the enzyme Pig Liver Esterase (PLE) for the resolution of racemic ethyl esters,[13] we tried to use this mild and selective biocatalyst for the *chemoselective* hydrolysis of the ethyl ester of enantiomerically pure **2.3**. Although lipases and esterases are most often used for the resolution of racemates (see chapters 5,6 and 7) in organic chemistry, there have been reports of their use as chemoselective catalysts as well. Examples can be found in peptide[14] and carbohydrate[15] chemistry. We indeed observed that in a phosphate-buffer (pH = 7.00) PLE was capable of hydrolyzing the ethyl ester of **2.3** without racemization. The acetylthio group of **2.3** was not hydrolysed so that (*R*)-2-acethylthio propanoic acid (**2.4**) could be isolated in a high yield (scheme 2.5).




**2.3** **2.4** **2.2**

*Scheme 2.5 Siteselective ester hydrolysis of **2.3** by PLE without racemization*

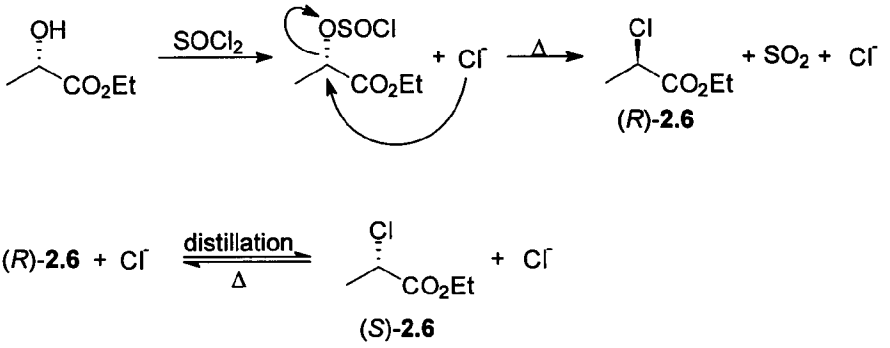
The observed preference for hydrolysis of the carboxylic ester of **2.3** is rather surprising because in enzymatic resolution experiments using Pig Pancreatic Lipase (PPL)[16] or lipases from *Pseudomonas sp.*[17] on analogous substrates, acetylthio groups are usually hydrolyzed preferentially. However, a report from the Mitsubishi company has appeared which describes that optically pure (-)-*β*-acetylmercaptoisobutyric acid (a precursor for Captopril, an ACE-inhibitor) can be prepared via preferential microbial carboxyl ester hydrolysis.[18] The **2.4** produced can be converted to the desired free thiol **2.2**, but also **2.2** can be prepared directly from **2.3** in a one pot procedure. Because our reaction is performed in an pH-autostat one can monitor the consumption of base, which is needed to neutralize the produced carboxylic acid. As the molarity of this added base is known the conversion of the reaction can be calculated at any stage. At the moment that exactly one equivalent of base has been added (**2.3** has been converted completely to **2.4**), 2N $NH_3$ is added and the reaction mixture is stirred for another 6 hours. Under these conditions the acetylthio group is hydrolyzed and (*R*)-thiolactic acid (**2.2**) is produced without racemization in an overall yield of >65% based on (S)-ethyl lactate (scheme 2.6).




*Scheme 2.6 Total synthesis of **2.2** from ethyl lactate featuring a one-pot hydrolysis procedure*

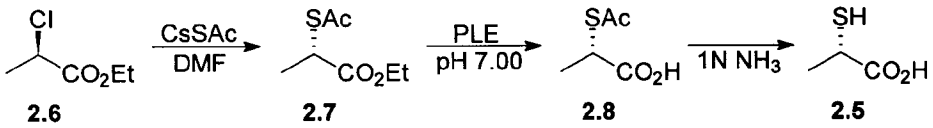
On prolongued standing **2.2**, however, slowly racemizes in contrast to natural lactic acid. We have tried to extend this methodology to produce the (*S*) form of thiolactic acid as well. Following the original Strijtveen procedure[7] one has to start from the unnatural (and very expensive) (D)-form of alanine to produce (*R*)-*α*-chloropropanoic acid, which can subsequently be converted to (*S*)-thiolactic acid (**2.5**). From an economical point of view this is of course not very interesting. To follow our procedure described above one has to start with the unnatural form of ethyl lactate, which is less readilly available, so both methodologies have serious drawbacks. Therefore, we searched for an alternative procedure to prepare (*S*)-thiolactic acid by means of a double inversion procedure from (*S*)-ethyl lactate. It is known that (*S*)-ethyl lactate can be converted to (*R*)-ethyl 2-chloropropionate (**2.6**) using either a large excess of $PCl_5$[19] or by treatment with $SOCl_2$.[20] However, the major drawback of both procedures is the low yield of the desired product. As the procedure using $SOCl_2$ seemed more easy we tried this approach. Exact repetition of the experimental conditions given, however, led to a product with an optical purity which decreased during distillation. This is not surprising if we take

a closer look at the mechanism of this inversion reaction (scheme 2.7).




*Scheme 2.7 Mechanism of synthesis and racemization of ethyl chloropropanoate*

In the original procedure[20] the reaction is not quenched with ice after reaction with excess of $SOCl_2$. Therefore, upon heating during distillation, chloride still present can attack (*R*)-**2.6** to give (*S*)-**2.6**. This means that the first fractions collected during distillation have high enantiomeric purity, but that fractions collected later have lower enantiomeric purity. This was indeed the case as was established by chiral GC. The total yield of desired product in optically pure form is therefore low. We have improved this procedure simply by adding ice after the reaction and isolating the product by extraction. As no chloride is present any more, the product is now easily obtained without the risk of racemization. In a total yield of 75% (*R*)-**2.6** could thus be produced with an e.e. of 95%. (*R*)-**2.6** can subsequently be inverted following the Strijtveen procedure with cesium thioacetate in DMF to give (*S*)-ethyl (acetylthio)propionate (**2.7**). Following our own procedure using PLE, this material can be hydrolyzed to the carboxylic acid **2.8** without racemization (scheme 2.8).



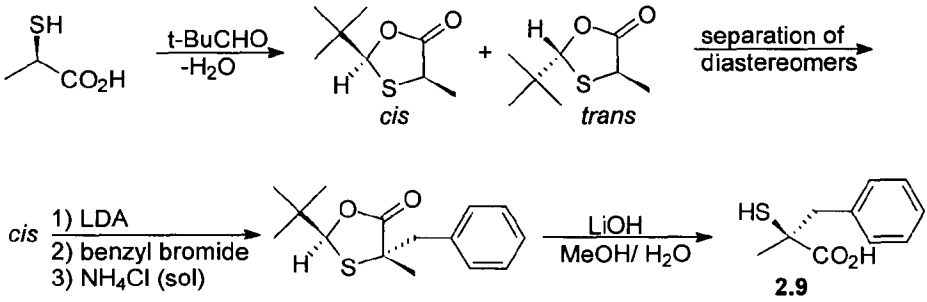

*Scheme 2.8 Synthesis of (S)-thiolactic acid from ethyl (R)-chloropropanoate*

Although this reaction is about two times slower as for the (*R*) enantiomer it is still chemoselective. Experiments using *racemic* ethyl (acetylthio)propionate showed indeed that chiral recognition using PLE as catalyst is only marginal. Following the known procedure (*S*)-**2.8** can be deacylated with ammonia to produce optically pure (*S*)-thiolactic acid (**2.5**). In this way **2.5** is obtained in 55% yield based on

**2.6**. The production of the (*S*)-enantiomer can be extended to a one pot procedure as well.

### 2.5 α-Alkylation of (*R*)-thiolactic acid

To produce optically pure tertiary α-mercapto acids from thiolactic acid one has to develop a method to substitute a proton at the chiral center for an alkyl group without loss of chirality. Direct substitution via deprotonation and subsequent alkylation would, of course, lead to a racemic product. Seebach has, however, developed a method in which such an alkylation can take place via transfer of the chirality to a newly formed chiral acetal center. This methodology,[21] which has been tested on several optically pure α-hydroxy acids and one racemic α-mercapto acid, was extended to the synthesis of optically pure α-alkylated α-mercapto acids by Strijtveen some years ago.[2] The methodology consists of condensing an α-mercapto acid with pivalaldehyde to yield a mixture of *cis*- and *trans*-1,3-oxathiolan-5-ones, which can be separated by fractional crystallization and column chromatography (scheme 2.9). The diastereomerically pure oxathiolanones produced can be deprotonated with a strong base such as LDA, which destroys the original chiral center. Upon alkylation with an electrophile the large t-butyl group on the acetal chiral center directs the diastereoselectively of alkylation to almost total pure *trans*-product. The diastereomerically pure α-alkylated oxathiolanone produced can subsequently be hydrolyzed to yield the tertiary α-mercapto acid. Starting from either the *cis*- or *trans*-1,3-oxathiolane-5-one both enantiomers of the desired α-alkylated α-mercapto acid can be prepared from one enantiomer of the starting α-mercapto acid.
By means of this methodology we have prepared optically pure (*S*)-α-benzylthiolactic acid (**2.9**) (scheme 2.9).




*Scheme 2.9 Preparation of optically pure α-alkylated α-mercapto acid* ***2.9*** *according to Strijtveen*

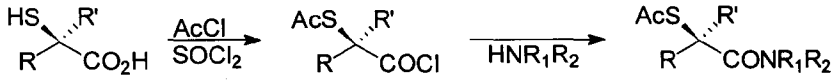
Although the described methodology is successful, it has some severe drawbacks. These are:

a) pivalaldehyde is an expensive reagent which has to be used in excess.
b) as condensation with pivalaldehyde is only moderately diastereoselective and preferential crystallization of one of the diastereomers is rather tedious, product recovery (by chromatography) is low.
c) preparation of a large variety of α-alkylated-α-mercapto acids following this strategy is time consuming and uneconomical, since some steps give only moderate chemical yields.

In view of these drawbacks we decided first to examine the potential of (*S*)-**2.9** as a precursor for the synthesis of new chiral tertiary β-amino thiols before investing a great deal of time in the preparation of analogs of **2.9**. A straightforward method to convert the α-mercapto acid to the β-amino thiol would be amidation of the α-mercapto acid to the amide, followed by reduction to give the amine.

### 2.6 Amidation of α-mercapto acids

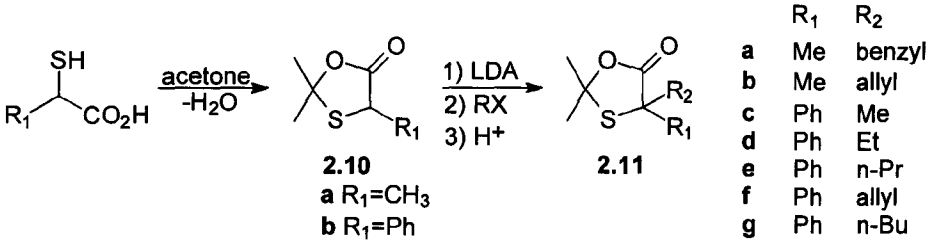
In the literature not much is known about the preparation of α-mercapto amides from the corresponding α-mercapto acids. Most literature procedures deal with the synthesis of derivatives of thioglycolic acid, the simplest α-mercapto acid available. As thioglycolic acid is not chiral, and steric hinderance does not play a role during amidation few problems are encountered. It is observed that amidation of this α-mercapto acid using several amines is spontaneous and complete within minutes in the absence of solvent.[22] Alternatively, amidation can be performed by azeotropic removal of water,[23] or by amidation of the ethyl ester of the thioglycolic acid.[24] Also amidation via an intermediate, unstable, acid chloride has been reported.[24] After testing of these procedures on *racemic* thiolactic acid, the most promising methodology appeared to be acylation of the mercapto group,[25] transformation of the carboxylic acid to the acid chloride followed by coupling with an amine (scheme 2.10).




*Scheme 2.10 Synthesis of tertiary α-mercapto amides from α-mercapto acids*

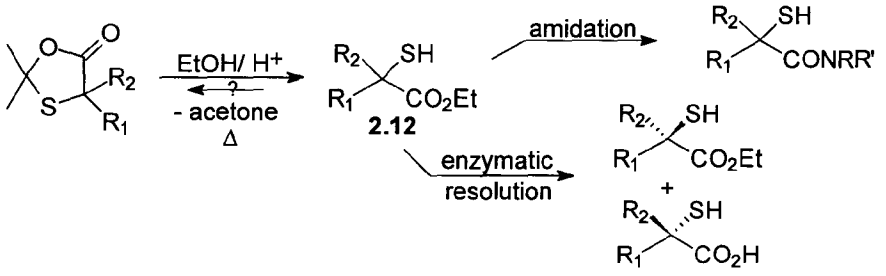
Unfortunately, the successful strategy for thiolactic acid failed for the preparation of an amide of α-alkylated-α-mercapto acid **2.9**, and only a black tar was obtained. Also direct condensations of **2.9** with an amine by azeotropic water removal were not successful; only the salt was produced. An alternative would be the use of a

dehydrating agent such as carbonyldiimidazole (CDI), which has been shown to be very effective in the amidation of an optically pure α-alkylated-α-hydroxy acid.[26] However, when we used this strategy with compound **2.9**, only starting material was recovered. Upon reaction of the α-mercapto acid with CDI probably the acidic thiol can form an ion pair with liberated imidazole, which is needed to form the activated intermediate. As this it no longer possible, no reaction takes place.
For reactivity studies, we prepared some racemic α-alkylated-1,3-oxathiolanones which are accessible via α-alkylation of the acetonides of the α-mercapto acids (scheme 2.11).



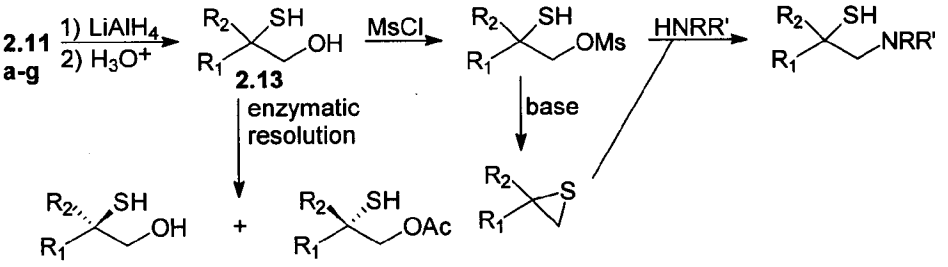

*Scheme 2.11 Synthesis of racemic α-alkylated oxathiolanones* ***2.11***

First, we tried to convert the α-alkylated oxathiolanones to the corresponding ethyl esters by acidic ethanolysis, as amides can be prepared by acylation of amines by α-mercapto esters. Also, these α-alkylated α-mercapto esters could be interesting substrates for enzyme catalyzed resolutions in analogy to the α-alkylated α-hydroxy acids (see chapter 1). Previously in our group, Moorlag had shown that α-alkylated α-hydroxy acids can be resolved efficiently by PLE.[27] However, the conversion of oxathiolanones to their esters, which is successful for the corresponding oxygen analogs, was only moderately successful because of extremely long reaction times. After 7 days around 50% conversion had taken place, and due to the harsh




*Scheme 2.12 Synthesis and resolution of tertiary α-mercapto acids*

conditions (acidic, prolonged heating) already much starting material had decomposed (scheme 2.12). Moreover, the produced α-mercapto esters have an extremely pungent smell. Probably the reverse reaction (acetalization) takes place as well due to the nucleophilicity of the produced thiol towards acetone. Also, direct amidation of the α-alkylated-1,3-oxathiolanones was fruitless.
An alternative would be to convert racemic α-alkylated-1,3-oxathiolaneones to β-mercapto alcohols by reduction. Subsequently, these alcohols could be converted to β-amino thiols by conversion of the alcohol to the amine via the mesylate (or thiirane). Also, there might be the possibility to resolve these mercapto alcohols in the antipodes by enzyme catalyzed resolution (scheme 2.13).

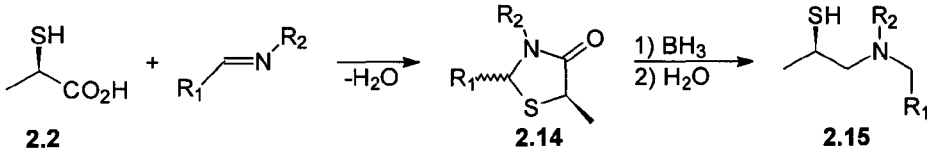



*Scheme 2.13* *Synthesis of tertiary β-mercapto alcohols **2.13** and theoretical conversion to the corresponding amines*

Indeed, **2.11** could be converted straightforwardly to the mercapto alcohols **2.13** by reduction using $LiAlH_4$. However, these compounds were rather smelly and hard to purify. Still, we investigated enzymatic resolution of these (sometimes not entirely pure) intermediates, but the attempts were unsuccessful. Only a few lipases (CCL, PPL, HPL and AY)[28] were capable of giving significant conversions but enantioselectivity was low ($E<3$); most lipases showed only initial reactivity which soon faded. Probably this has something to do with the thiol group, which might give substrate inhibition by disulfide linkage to the peptide. This idea was checked by sustitution of the mercapto group of **2.13** for a hydroxyl group. Indeed α-alkylated diols are resolved nicely by lipases; these results are described in detail in chapter 6.
Due to all the problems encountered in preparing tertiary β-amino thiols, we decided to drop our initial proviso that the chiral center had to be tertiary and focussed our attention on a simpler system, namely secondary β-amino thiols directly derived from (*R*)-thiolactic acid and β-amino thiols derived from ephedra alkaloids (see chapter 3).

## 2.7 1,3-Thiazolidin-5-ones derived from thiolactic acid

As stated in the previous section, it is not easy to directly convert α-mercapto acids other than thioglycolic acid to amides. However, α-mercapto acids can be converted to thiazolidinones by condensation with imines (derived from an amine and an aldehyde) very straightforwardly.[29] Also, a paper has appeared in which it is claimed that thiazolidinones can be reduced by $LiAlH_4$ to the corresponding β-amino thiols.[30] This strategy of condensation of α-mercapto acids with imines and subsequent reduction therefore seemed a very promising alternative to make new chiral ligands derived from (*R*)-thiolactic acid (scheme 2.14).




**2.2** **2.14** **2.15**

*Scheme 2.14 Synthesis of thiazolidinones* ***2.14*** *from thiolactic acid by cyclocondensation*

As imines can be prepared *in situ* from an aldehyde and an amine, we performed these reactions by mixing the three reagents and remove the formed water by azeotropic distillation. As a new chiral center is formed during the reaction, always a mixture of diastereomers is produced. Upon reduction, the new chiral center is, however, lost. To get acquainted with the technology, we first did some test experiments using racemic thiolactic acid as starting material. Results from the condensations are collected in table 1.

**Table 1. Cyclocondensations of thiolactic acid to thiazolidinones 2.14**

| entry | compound | $R_1$ | $R_2$ | yield (%) | d.e. (%) |
|---|---|---|---|---|---|
| 1 | **2.14a** | i-propyl | phenyl | 70 | 33 |
| 2 | **2.14b** | phenyl | phenyl | 68 | 11 |
| 3 | **2.14c** | t-butyl | phenyl | 18 | 60 |
| 4 | **2.14d** | 2-pyridyl | phenyl | 68 | 91 |
| 5 | **2.14e** | t-butyl | H | 72 | 43 |
| 6 | **2.14f** | i-propyl | H | 32 | >99[a] |
| 7 | **2.14g**[29a] | phenyl | methyl | n.d. | 60 |

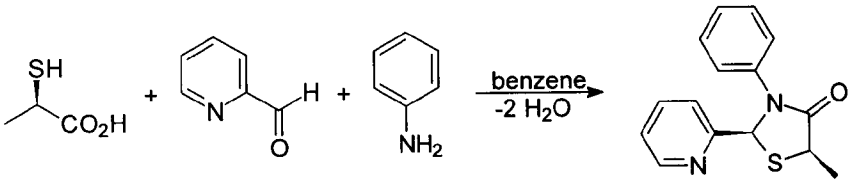
a) Yield and d.e. after crystallization.

We tried to perform the same condensations with thiolactic acid and aniline using ketones (acetone, benzophenone) instead of aldehydes, but yields of these reactions were considerably lower due to lower reactivity of the ketone and/or formed imine.

Reduction of the thiazolidinone **2.14a** using $LiAlH_4$ analogous to reference 30 gave, in addition to the desired compound, undesired decomposition (such as desulfurization) of the starting material. The use of diborane as reducing agent was more successful, and the desired β-amino thiol **2.15a** was isolated in good yield.Therefore we performed the same reaction with optically pure (*R*)-thiolactic acid. Thiazolidinone (R)-**2.14a** was obtained in good yield as a 1:2 mixture of *cis*- and *trans*-diastereomers (as judged by 200 MHz $^1H$ NMR). Also subsequent reduction with borane was successful and the (*R*)-β-amino thiol **2.15a** could be isolated as a clear oil in 78% yield (scheme 2.14). Surprisingly, this amino thiol is not easily oxidized to the disulfide as is the case for most other amino thiols (see chapter 3). On testing in catalytic asymmetric reactions this simple ligand was shown to give rather good enantiomeric inductions (see chapter 4) and therefore we are now expanding this methodology to other substrates.

In the specific condensation of scheme 2.14 there are 3 reagents which can be varied, so in principle a wide variety of β-amino thiols are accessible. Analogously to the racemic case, condensation with benzaldehyde instead of i-butyraldehyde proceeded cleanly to give adduct (*R*)-**2.14b** (entry 2). An even more interesting compound (from a ligand point of view) was prepared by condensation of (*R*)-**2.2** with 2-pyridinecarboxaldehyde (scheme 2.15). This thiazolidine might even be a nice ligand before reduction due to the possible donating properties of the pyridine moiety. Analogous chiral thiazolidinones have been used by Brunner *et al.* for Rh(I) catalyzed enantioselective hydrosilylations of ketones.[31]

Whereas condensation with most aldehydes is not very selective, the condensation of scheme 2.15 proceeds, however, with an diastereomeric excess of 91%. Diastereomerically pure material was obtained by a single recrystallization. Also we have substituted (*R*)-thiolactic acid for another optically pure α-mercapto acid. Previously Strijtveen has shown that optically active α-mercapto acids are



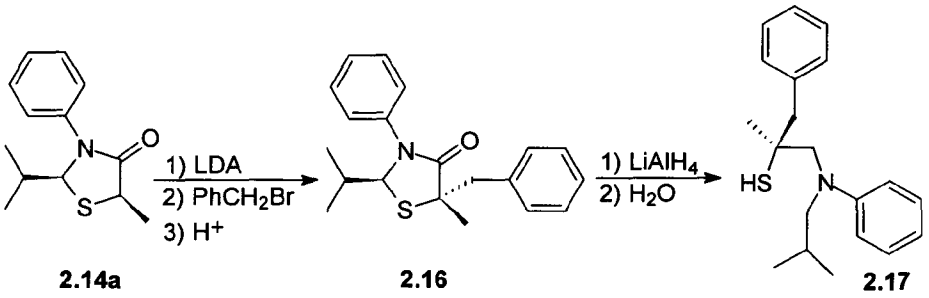

**2.14d**
d.e. 91%

*Scheme 2.15 Diastereoselective cyclocondensation of (R)-thiolactic acid with 2-pyridinecarboxaldehyde and aniline*

accessible from natural occurring amino acids.[7] In this way we are able to increase the steric bulk at the chiral center by using valine or phenylalanine as starting material. This increase in steric bulk would certainly have influence on the diastereomeric excess of cyclocondensation. Also positive effects can be expected on the catalytic activity in the diethylzinc reaction after reduction of the new thiazolidinones to the corresponding β-amino thiols. Work on this specific topic is currently under progress by Danny Staal, and hopefully results will be published in the near future.

## 2.8 α-Alkylation of 1,3-thiazolidin-5-ones

As has been shown in the previous sections of this chapter it is relatively easy to convert α-mercapto acids to the corresponding thiazolidinones. Also reduction to β-amino-thiols generally goes without problems. We now wondered whether we could achieve our initial goal, the synthesis of tertiary β-mercapto amines, via the α-alkylation of thiazolidinones **2.14**. This has the advantage that we would already have built in the nitrogen functionality, which could not be incorporated in an α-alkylated α-mercapto acid via the Strijtveen methodology. The major problem we were concerned with was the diastereomeric induction from the acetal chiral center upon α-alkylation. As we had a reasonable quantity of racemic thiazolidinone **2.14a** available as a mixture of *cis*- and *trans*-diastereomers, we examined whether the isopropyl group on the acetal center was large enough to give reasonable induction upon α-alkylation. We found that alkylation with benzyl bromide proceeded smoothly, and that using 200 MHz $^1$H-NMR only one diastereomer (*trans*) could be detected. This is a major improvement because expensive pivalaldehyde can now be avoided. This result encouraged us to test the possibility of alkylating optically pure **2.14a** under the same experimental conditions. However, before alkylation the *cis*- and *trans*-diastereomers had to be separated. Several solvents (eg. EtOH, MTBE, EtOAC/hexane) were examined to resolve the diastereomers by




**2.14a** **2.16** **2.17**

*Scheme 2.16 Diastereospecific alkylation of optically pure thiazolidinone **2.14** with benzylbromide*

recrystallization, but efforts remained unsuccessful, although small diastereomeric enrichment was observed. The only way in which the diastereomers could be separated was by radial chromatography (chromatotron), which provided us with samples of several hundred milligrams of both diastereomers. The major *cis*-diastereomer of (*R*)-**2.14** was subsequently alkylated with benzyl bromide to give the α-alkylated thiazolidinone **2.16** in > 98% diastereomeric excess (scheme 2.16). In principle, **2.16** gives after reduction, in analogy to compound **2.14a**, the optically pure tertiary β-amino thiol **2.17**. In this way we would finally have fulfilled our initial goal; the synthesis of tertiary optically pure β-amino thiols.

## 2.9 Conclusions

We have shown that (*R*)-thiolactic acid is a versatile building block in asymmetric synthesis. Previously, the access to this useful intermediate was uneconomical due to the multistep synthetic procedure needed, giving the product in only moderate yield. The new route, based on optically pure ethyl lactate and mild ester hydrolysis by PLE, is superior both in yield and price of reagents. Also this strategy is easily expanded to the synthesis of (*S*)-thiolactic acid. Unfortunately, the conversion of α-alkylated derivatives of thiolactic acid to the corresponding β-mercapto amines via several routes was unsuccessful. This initial goal was therefore dropped and efforts were undertaken to convert (*R*)-thiolactic acid to secondary β-mercapto amines. A nice route via the crystalline thiazolidinones was found, opening the way to numerous new chiral β-amino thiols. This work is currently under progress and initial results have shown that these molecules are indeed efficient chiral catalysts in the 1,2 addition of diethylzinc to benzaldehyde (see chapter 4). Also, we have shown that, in principle, tertiary β-mercapto amines are available in optically pure form as well via this route by diastereospecific alkylation of thiazolidinones followed by reduction.

**Acknowledgement**

Danny Staal is gratefully acknowledged for several of the experiments described in section 2.7 of this chapter. A generous gift of PLE from Amano Enzyme Europe Ltd. is acknowledged as well.

## 2.10 Experimental

**General**

All solvents were reagent grade and were dried and distilled prior to use, following standard procedures. All reagents were purchased from either Acros chimica (previously Janssen chimica), Aldrich, Merck or Fluka and used without purification unless stated otherwise. Melting points (uncorrected) were determined on a Mettler FP21 melting point apparatus equipped with a Mettler FP2 microscope. Optical

rotations were determined at room temperature using a Perkin-Elmer 241 polarimeter and are given in units of $10^{-1}$ deg $cm^2$ $g^{-1}$. $^1H$ NMR Spectra were recorded at room temperature on either a Varian Gemini-200 (200 MHz) or Varian VXR-300 (300 MHz) spectrometer. Chemical shifts are denoted in $\delta$ units (ppm), relative to tetramethylsilane (TMS) as internal standard or relative to residual solvent peaks. $^{13}C$ NMR spectra (APT) were recorded on either a Varian Gemini-200 (50.32 MHz) or Varian VXR-300 (75.48 MHz) spectrometer. Chemical shifts are denoted in $\delta$ units (ppm) relative to $\delta(CDCl_3)$ = 76.91 ppm. $^{19}F$ NMR spectra were recorded on a Varian Gemini-200 (188.143 MHz) spectrometer and are denoted in $\delta$ units (ppm), relative to $\delta(CFCl_3)$ = 0 ppm. HPLC analysis was carried out using a Waters 600 HPLC system equipped with a Waters 600E system controller and a Waters 991 photodiode array detector; Millennium™ 2010 chromatography manager was used as system software. GC analysis was carried out using a Hewlett-Packard 5890A gas chromatograph equipped with a Hewlett-Packard 3396 series II integrator. Mass spectra were recorded on an AEI-MS-902 mass spectrometer by EI by Mr. A. Kiewiet in our department. Elemental analysis were performed in the microanalytical group of this department by Mr. H. Draaijer, Mr. J. Ebels and Mr. J. Hommes.

PLE was obtained from Amano Enzyme Europe Ltd. and was used as such. Enzymatic hydrolysis reactions were performed with a Radiometer PHM 82 pH stat, equipped with a TTT 80 titrator and an ABU 80 autoburette.

**(*R*)-2-(Acetylthio)propanoic acid (2.4)**
In 50 ml of phosphate buffer (pH 7.00) ethyl (*R*)-2-(acetylthio)propanoate (**2.3**)[7] (2.06 g, 11.7 mmol) was suspended with PLE (50 mg) under vigorous stirring; the pH of the solution was kept at 7.00 by continuous addition of 2N aqueous NaOH by means of an autoburette. After addition of the theoretical amount of base (22 h) the reaction mixture was acidified by addition of 2N aqueous HCl. Ether (150 ml) was added and the mixture was filtered over celite to remove the remaining enzyme. The organic layer was separated, and the water layer was extracted three times with ether. After washing with brine and drying ($Na_2SO_4$) the organic layer was evaporated and **2.4** (1.54 g, 10.4 mmol, 89 %) was obtained as an oil, which was purified by bulb-to-bulb distillation (b.p. 115°/0.3 mm Hg), $[\alpha]_D$ = +136° (c, 1.06 in $CHCl_3$) [lit.[5] $[\alpha]_D$ = +137° (c, 3.9 in $CHCl_3$)]; o.p. >98%.

**One pot procedure for the preparation of (*R*)-2-mercaptopropanoic acid (2.2)**
Compound **2.3** (5.00 g, 28.4 mmol) was suspended in a pH 7.00 phosphate buffer (60 ml) and PLE (100 mg) was added under vigorous stirring; the pH of the suspension was kept at 7.00 by continuous addition of 2N aqueous NaOH. After 46 h the theoretical amount of base had been consumed and 2N aqueous $NH_3$ (60 ml) was added. After stirring for another 5 h ether (150 ml) was added and the mixture was filtered over celite. The celite was thoroughly washed with ether and

the organic layer was separated. The water layer was extracted three times with ether and the combined organic layers were washed with brine and dried over $Na_2SO_4$. After evaporation (*R*)-**2.2** was obtained (2.97 g, 28.0 mmol, 99%) as a slightly yellow oil. After bulb-to-bulb distillation (120°/15 mm Hg) a pure sample was obtained with identical properties to a sample prepared according to ref 7, $[\alpha]_D$ = + 56.5° (c, 4.17 in EtOAc); o.p.> 98%.

**Ethyl (*R*)-2-chloropropanoate (2.6)**
To neat ethyl (*S*)-lactate (50 g, 424 mmol) containing DMF (0.3 ml) was carefully added neat $SOCl_2$ (33 ml). The mixture was refluxed until the evolution of $SO_2$ ceased (3 h). The crude mixture was poured on ice and was extracted three times with ether. The ether solution was washed with brine and dried ($MgSO_4$) and the ether was evaporated under reduced pressure at room temperature. The resulting yellow oil was distilled to provide **2.6** (43.6 g, 319 mmol, 75%) as a colourless oil ; b.p. 143-145°; e.e. 95% (chiral GLC, 50m WCOT fused silica capillary GC column coated with CP cyclodextrin-B-2,3,6-M-19 (Chrompack No. 7501)); $[\alpha]_D$ = +19.1° (neat) (lit[20] +19.8°); o.p. 96%.

**Ethyl (*S*)-2-(acetylthio)propanoate (2.7)**
This compound was prepared from **2.6** following the same procedure as described for the (*R*) enantiomer in reference 7; $[\alpha]_D$ = -132.9° (c, 4.90 in $CHCl_3$); o.p. 97%. All other physical properties were in accordance with the known enantiomer **2.3**.

**(*S*)-2-(Acetylthio)propanoic acid (2.8)**
In a procedure analogous to that described above for **2.4**, **2.7** (2.06 g, 11.7 mmol) was converted at pH 7.00 with PLE (50 mg) in 39 h to give crude **2.8** containing traces of (*R*)-**2.2**. Pure **2.8** (1.31 g, 8.85 mmol, 76%) was isolated by bulb-to-bulb distillation (b.p. 95°/ 0.08 mm Hg); $[\alpha]_D$ =-135.5° (c, 4.35 in $CHCl_3$); o.p. >98%; All other physical properties were in accordance with the known enantiomer **2.4**.

**(*S*)-2-Mercaptopropanoic acid (2.5)**
Compound **2.8** (870 mg, 5.88 mmol, o.p. 95%) was stirred for 5h in 2N aqueous $NH_3$ (20 ml). After acidification with 2N aqueous HCl the mixture was extracted three times with ether. The combined organic layers were washed with brine and dried ($Na_2SO_4$). After evaporation the remaining yellow oil was bulb-to-bulb distilled to yield (*S*)-**2.5** (510 mg, 4.81 mmol, 82%); b.p. 130°/ 15 mm Hg; $[\alpha]_D$ =-54.3° (c, 5.76 in EtOAc); o.p. 95%. All other physical properties were in accordance with the known enantiomer (*R*)-**2.2**.

**(*S*)-2-methyl-2-mercapto-3-phenylpropanoic acid (2.9)**
This compound was prepared by a multistep procedure from **2.2** as described by Strijtveen.[2]

**2,2,4-Trimethyl-[1,3]oxathiolan-5-one (2.10a)**
(*R,S*)-Thiolactic acid (5.0 g, 47 mmol) and acetone (5.47 g, 94 mmol) were refluxed overnight in benzene (100 ml) in the presence of a catalytic amount of TsOH in a Dean-Stark apparatus. After cooling the mixture was washed with water and brine and dried ($Na_2SO_4$). After evaporation there remained **2.10a** (6.58 g, 45 mmol, 96%) as a slightly yellow oil which was bulb-to-bulb distilled (110 °C/ 15 mm Hg, lit.[32] 82 °C/ 14 mm Hg) to give completely pure material. $^1$H NMR ($CDCl_3$): $\delta$ 1.56 (d, J = 6.6 Hz, 3H), 1.72 (s, 3H), 1,75 (s, 3H), 4.11 (q, J = 6.6 Hz, 1H); $^{13}$C NMR ($CDCl_3$): $\delta$ 17.84 (q), 30.75 (q), 31.29 (q), 42.45 (d), 86.15 (s), 174.94 (s).

**2,2-Dimethyl-4-phenyl-[1,3]oxathiolane-5-one (2.10b)**
Thiolacetic acid (10.6 g, 139.5 mmol) was dissolved in 150 ml of MeOH. $K_2CO_3$ (9.65 g, 69.8 mmol) was added in small portions. After reaction ceased, $\alpha$-bromophenylacetic acid (30.0 g, 140 mmol) was added and the mixture was stirred overnight. The mixture was evaporated to dryness and redissolved in ether. The KCl formed was removed by filtration and the salts were washed with ether. The filtrate was evaporated to give a quantitative yield of 2-(acetylthio)phenylacetic acid. This was purified by recrystallization from ether/hexane to give colourless needles (28.1 g, 134 mmol, 96%). Part of this thioacetate (15.0 g, 71.4 mmol) was dissolved in ammonia (1N, 300 ml) and stirred overnight. The mixture was acidified with 2N HCl and extracted four times with ether. The combined organic layers were washed with brine and dried ($Na_2SO_4$). After evaporation there remained 2-mercapto-phenylacetic acid ('thiomandelic acid') (11.28 g, 67.1 mmol, 94%). This material was dissolved in benzene (100 ml) together with acetone (8.7 g). A droplet $H_2SO_4$ was added and the mixture was refluxed azeotropically in a Dean-Stark apparatus for 5h. The mixture was washed with water and brine and subsequently dried ($Na_2SO_4$). After evaporation there remained an off-white powder (13.42 g, 64.5 mmol, 96%), which was recrystallized from benzene/hexane to provide pure **2.10b**; mp 86.0-87.0 °C; $^1$H NMR ($CDCl_3$): $\delta$ 1.86 (s, 6H), 5.28 (s, 1H), 7.34-7.51 (m, 5H); $^{13}$C NMR ($CDCl_3$): $\delta$ 30.85 (q), 31.61 (q), 52.59 (d), 128.45 (d), 128.54 (d), 128.76 (d); Anal. Calcd for $C_8H_8O_2S$: C, 63.43; H, 5.81; S, 15.39. Found: C, 63.34; H, 5.79; S, 15.39.

**General procedure for the $\alpha$-alkylation of oxathiolanones 2.10**
In an atmospere of nitrogen in dried glassware oxathiolanone **2.10b** (5.00 g, 24 mmol) was dissolved in 50 ml of THF. The mixture was cooled to -20 °C and KOtBu (2.91 g, 26 mmol) was added. The mixture was stirred for 5 min (all the KOtBu had dissolved and the solution had turned orange) and alkyl halide (30 mmol) in THF was added dropwise. The mixture was stirred overnight and saturated $NH_4Cl$ solution was added. The mixture was extracted three times with ether and the combined organic layers were washed with brine. After drying ($Na_2SO_4$) and evaporation of the solvent there remained a nearly quantitative yield of $\alpha$-alkylated

product **2.11** which was purified by distillation.
For **2.10a** an analogous procedure was employed, except that LDA was used as base and the enolate was generated at -80°C.

**4-Benzyl-2,2,4-trimethyl-[1,3]oxathiolan-5-one (2.11a)**
Following the general procedure there was obtained from **2.10a** (5.0 g, 34.2 mmol) and benzyl bromide a quantitative yield of crude **2.11a**. This was purified by bulb-to-bulb distillation to give a colourless oil (6.82 g, 28.9 mmol, 84%, bp 95°C/ 0.3 mm Hg); $^1$H NMR ($CDCl_3$): $\delta$ 1.19 (s, 3H), 1.68 (s, 3H), 1.72 (s, 3H), 2.93 (d, J = 14 Hz, 1H), 3.30 (d, J = 14 Hz, 1H), 7.16-7.39 Hz (m, 5H); $^{13}$C NMR ($CDCl_3$): $\delta$ 29.72 (q), 31.83 (q), 33.50 (q), 46.95 (t), 59.40 (s), 84.96 (s), 127.19 (d), 127.99 (d), 130.84 (d), 136.05 (s).

**4-Allyl-2,2,4-trimethyl-[1,3]oxathiolane-5-one (2.11b)**
Following the general procedure there was obtained from **2.10a** (5.0 g, 34.2 mmol) and allyl bromide a quantitative yield of crude **2.11b**. This was purified by bulb-to-bulb distillation to give a colourless oil (5.29 g, 28.4 mmol, 83%, bp 50°C/ 0.01 mm Hg); $^1$H NMR ($CDCl_3$): $\delta$ 1.65 (s, 3H), 1.76 (s, 3H), 1.78 (s, 3H), 2.47-2.71 (m, 2H), 5.12-5.27 (m, 2H), 5.70-5.93 (m, 1H); $^{13}$C NMR ($CDCl_3$): $\delta$ 28.51 (q), 32.45 (q), 33.28 (q), 45.49 (t), 57.29 (s), 84.84 (s), 119.95 (t), 132.33 (d).

**2,2,4-Trimethyl-4-phenyl-[1,3]oxathiolane-5-one (2.11c)**
Following the general procedure there was obtained from **2.10b** (5.0 g, 24 mmol) and methyl iodide crude **2.11c** (4.30 g, 19.4 mmol, 81%). This was purified by bulb-to-bulb distillation (bp 110°C/ 1 mm Hg) to give pure **2.11c** (3.27 g, 14.7 mmol, 61%). The moderate yield is due to careless work-up; $^1$H NMR ($CDCl_3$): $\delta$ 1.48 (s, 3H), 1.79 (s, 3H), 1.93 (s, 3H), 7.23-7.42 (m, 3H), 7.58-7.66 (m, 2H); $^{13}$C NMR ($CDCl_3$): $\delta$ 30.43 (q), 31.33 (q), 85.27 (s), 125.79 (d), 127.52 (d), 128.57 (d), 141.95 (d).

**4-Ethyl-2,2-dimethyl-4-phenyl-[1,3]oxathiolane-5-one (2.11d)**
Following the general procedure there was obtained from **2.10b** (10.0 g, 48 mmol) and ethyl iodide crude **2.11d** (10.68 g, 45.3 mmol, 94%), which was purified by bulb-to-bulb distillation (bp 90°C/ 0.01 mm Hg) to give a colourless oil (9.32 g, 39.5 mmol, 83%); $^1$H NMR ($CDCl_3$): $\delta$ 0.89 (t, J = 7.3 Hz, 3H), 1.45 (s, 3H), 1.76 (s, 3H), 2.20 (dq, 2H), 7.26-7.39 (m, 3H), 7.68-7.73 (m, 2H); $^{13}$C NMR ($CDCl_3$): $\delta$ 10.47 (q), 31.13 (q), 31.76 (q), 36.27 (t), 66.70 (s), 85.52 (s), 126.61 (d), 127.79 (d), 128.42 (d), 140.29 (s), 174.53 (s); HRMS calcd m/z 236.087. Found 236.087; Anal. Calcd for $C_{13}H_{16}SO_2$: C, 66.07; H, 6.82; S, 13.57. Found: C, 65.93; H, 6.83; S, 13.60.

**2,2-Dimethyl-4-phenyl-4-propyl-[1,3]oxathiolane-5-one (2.11e)**
Following the general procedure there was obtained from **2.10b** (5.0 g, 24 mmol)

and n-propyl iodide crude **2.11e** (5.56 g, 22.2 mmol, 93%), which was purified by bulb-to-bulb distillation (bp 95°C/ 0.35 mm Hg); $^1$H NMR ($CDCl_3$): $\delta$ 0.87 (t, J = 8 Hz, 3H), 1.09-1.44 (m, 2H), 1.47 (s, 3H), 1.79 (s, 3H), 2.16 (m, 2H), 7.24-7.42 (m, 3H), 7.68-7.78 (m, 2H); $^{13}$C NMR ($CDCl_3$); $\delta$ 13.87 (q), 19.52 (t), 31.14 (q), 31.71 (q), 45.28 (t), 66.12 (s), 85.65 (s), 126.59 (d), 127.75 (d), 128.42 (d), 140.55 (s); HRMS calcd m/z 250.103. Found 250.103.

**4-Allyl-2,2-dimethyl-4-phenyl-[1,3]oxathiolane-5-one (2.11f)**
Following the general procedure there was obtained from **2.10b** (10.0 g, 48 mmol) and allyl bromide a nearly quantitative yield of crude **2.11b**. This was purified by bulb-to-bulb distillation (bp 90°C/ 0.06 mm Hg) to give a colourless oil (11.21 g, 45.2 mmol, 94%); $^1$H NMR ($CDCl_3$): $\delta$ 1.45 (s, 3H), 1.76 (s, 3H), 2.93 (m, 2H), 4.99-5.14 (m, 2H), 5.45-5.68 (m, 1H), 7.24-7.39 (m, 3H), 7.65-7.74 (m, H); $^{13}$C NMR ($CDCl_3$): $\delta$ 30.95 (q), 31.68 (q), 46.99 (t), 65.20 (s), 85.80 (s), 119.49 (t), 126.55 (d), 127.79 (d), 128.34 (d), 132.32 (d), 139.74 (s), 173.87 (s); HRMS calcd m/z 248.087. Found 248.087; Anal. Calcd for $C_{14}H_{16}SO_2$: C, 67.71; H, 6.49; S, 12.91. Found: C, 67.38; H, 6.44; S, 13.01

**4-Butyl-2,2-dimethyl-4-phenyl-[1,3]oxathiolane-5-one (2.11g)**
Following the general procedure there was obtained from **2.10b** (3.0 g, 14.4 mmol) and n-butyl iodide a nearly quantitative yield of crude **2.11g**, which was purified by bulb-to-bulb distillation (bp 135°C/ 0.5 mm Hg) to give a colourless oil (2.97 g, 11.3 mmol, 78%); $^1$H NMR ($CDCl_3$): $\delta$ 0.84 (dt, 3H), 1.18-1.31 (m, 4H), 1.46 (s, 3H), 1.78 (s, 3H), 2.17 (t, J = 8 Hz, 2H), 7.27-7.40 (m, 3H), 7.70-7.75 (m, 2H); $^{13}$C NMR ($CDCl_3$): $\delta$ 13.80 (q), 22.54 (t), 28.27 (t), 31.14 (q), 31.73 (q), 42.99 (t), 66.11 (s), 85.79 (s), 126.61 (d), 127.74 (d), 128.42 (d), 140.27 (s); HRMS calcd m/z 264.118. Found 264.118.

**General procedure for the reduction of oxathiolanes 2.11 to the corresponding β-mercapto alcohols 2.13**
In an atmosphere of nitrogen in dried glassware $LiAlH_4$ (912 mg, 24 mmol) was suspended in 50 ml of THF. Oxathiolanone **2.11** (8 mmol) was dissolved in 10 ml of THF and added dropwise to the suspension. The mixture was refluxed for 3h and subsequently quenched by the carefull dropwise addition of a saturated $NH_4Cl$ solution. Salts were filtered over celite which was extensively washed with ether. The organic layer was washed with brine and dried ($Na_2SO_4$). After evaporation a nearly quantitative yield of crude **2.13** was obtained, which was purified by distillation. *CAUTION: All β-mercapto alcohols **2.13** are extremely vile smelling oils. The odour both penetrates and clings; all glassware should be kept in the hood until cleaned by oxidation (bleach or peroxide).*

**2-Mercapto-2-phenyl-propan-1-ol (2.13c)**
Following the general procedure described above there was obtained from **2.11c**

(1.82 g, 8.2 mmol) crude **2.13c** (1.38 g, 8.2 mmol, 100%) which was not further purified; $^1$H NMR ($CDCl_3$): $\delta$ 1.78 (s, 3H), 2.17 (br, 1H), 2.62 (br, 1H), 3.83 (m, 2H), 7.24-7.60 (m, 5H).

**2-Mercapto-2-phenyl-butan-1-ol (2.13d)**
Following the general procedure described above there was obtained from **2.11d** (3.07 g, 13 mmol) crude **2.13d** (1.97 g, 10.8 mmol, 83%) which was purified by distillation (bp 110°C/ 0.45 mm Hg); $^1$H NMR ($CDCl_3$): $\delta$ 0.85 (t, J = 7.3 Hz, 3H), 1.96-2.14 (m, 3H), 2.34 (br, 1H), 3.83 (d, $J_{AB}$ = 11.4 Hz, 1H), 3.95 (d, $J_{AB}$ = 11.3 Hz), 7.22-7.55 (m, 5H); $^{13}$C NMR ($CDCl_3$): $\delta$ 8.92 (q), 33.25 (t), 57.80 (s), 70.46 (t), 126.84 (d), 128.16 (d), 141.99 (s).

**2-Mercapto-2-phenyl-pentan-1-ol (2.13e)**
Following the general procedure described above there was obtained from **2.11e** (3.00 g, 12 mmol) crude **2.13e** (1.81 g, 9.23 mmol, 77%), which was purified by distillation (bp 125°C/ 0.9 mm Hg). The moderate yield can be ascribed to a too enthusiastic work-up procedure; $^1$H NMR ($CDCl_3$): $\delta$ 0.90 (t, J = 6.7 Hz, 3H), 1.12-1.42 (m, 2H), 1.89-2.13 (m, 3H), 2.30 (br, 1H), 3.84 (d, $J_{AB}$ = 11.1 Hz, 1H), 3.98 (d, $J_{AB}$ = 11.1 Hz, 1H), 7.22-7.60 (m, 5H); $^{13}$C NMR ($CDCl_3$): $\delta$ 14.24 (q), 17.89 (t), 42.61 (t), 57.44 (s), 71.20 (t), 127.05 (d), 128.22 (d), 142.67 (s).

**2-Mercapto-2-phenyl-pent-4-ene-1-ol (2.13f)**
Following the general procedure described above there was obtained from **2.11f** (4.96 g, 20 mmol) crude **2.13f** (3.40 g, 17.5 mmol, 88%). Upon distillation (bp 140°C/ 0.05 mm Hg) this material decomposed. From the $^1$H NMR it was clear that signals in the allylic region were missing. Probably, upon heating, the thiol can give 1,2 addition to the alkene and form dimers.

**2-Isopropyl-5-methyl-3-phenylthiazolidin-4-one (2.14a)**
Aniline (2.73 ml, 30 mmol), thiolactic acid (2.66 ml, 30 mmol) and isobutyraldehyde (2.16 g, 30 mmol) were azeotropically refluxed in 100 ml of benzene for 4h. The mixture was evaporated to dryness to give crude **2.14a** (2:1 mixture of diastereomers as judged by 200 MHz $^1$H-NMR). This was recrystallized from EtOH to give colourless glistening needles (4.96 g, 21.1 mmol, 70%); mp 142.5-149.6°C; $^1$H NMR ($CDCl_3$): $\delta$ 0.85-0.95 (ddd, 6H, major and minor); 1.59 (d, J = 7.0 Hz, 3H, minor); 1.65 (d, J = 7.1 Hz, 3H, major), 1.93-2.11 (m, 1H, major and minor), 3.90-4.03 (dq, J = 7.0 Hz and J = 1.8 Hz, 1H, minor); 3.99 (q, J = 7.1Hz, 1H, major), 5.11 (dd, J = 3.2 Hz and J = 1.7 Hz, 1H, minor), 5.28 (d, J = 3.1 Hz, 1H, major), 7.27-7.48 (m, 5H, major and minor); $^{13}$C NMR ($CDCl_3$): $\delta$ 13.89 (q), 18.82 (q), 18.69 (q), 19.44 (q), 20.69 (q), 29.11 (d), 30.89 (d), 40.99 (d), 41.71 (d), 67.68 (d), 125.90 (d), 126.08 (d), 127.25 (d), 129.28 (d), 129.34 (d), 137.64 (s); Anal. Calcd for $C_{13}H_{17}NOS$: C, 66.35; H, 7.28; N, 5.95; S, 13.62. Found: C, 66.47; H, 7.17; N, 5.92; S, 13.64.

**(2*R*,5*R*)- and (2*S*,5*R*)-2-Isopropyl-5-methyl-3-phenylthiazolidin-4-one (2.14a)**
(*R*)-Thiolactic acid (2.97 g, 28 mmol), isobutyraldehyde (2.01 g, 28 mmol) and aniline (2.60 g, 28 mmol) were azeotropically refluxed overnight in 100 ml of benzene. After evaporation there remained an off white powder which was recrystallized from EtOH to give pure **2.14a** as a 1.5:1 mixture of diastereomers (4.51 g, 19.2 mmol, 69%). Physical data were in accordance with its racemate. A portion of this material (960 mg) was resolved in the diastereomers by radial chromatography (silica, ether/hexane 1:5). The first eluted diastereomer was the minor one (223 mg), the second being the major one (422 mg). Also a mixed fraction of 210 mg was obtained (total recovery 89%); Both components showed a d.e. > 99% by GC; mp 104-105.3 °C (minor); mp 114-114.9 °C (major). In analogy with cyclocondensations of $\alpha$-mercapto acids and $\alpha$-hydroxy acids with aldehydes the minor diastereomer is presumably the *trans* (2*R*,5*R*), and the major diastereomer the *cis* (2*S*,5*R*); Noesy experiments confirm this assumption.

**2,3-Diphenyl-5-methyl-thiazolidin-4-one (2.14b)**
Aniline (2.79 g, 30 mmol), thiolactic acid (3.18 g, 30 mmol) and benzaldehyde (3.18 g, 30 mmol) were refluxed azeotropically overnight in a Dean-Stark apparatus in 100 ml benzene. The mixture was evaporated to dryness and the resulting brown oil was recrystallized from EtOH to give **2.14b** (diastereomeric ratio 5:4 as judged by 200 Mhz $^1$H-NMR) (5.48 g, 20.3 mmol, 68%); mp 103.5-104.5 °C; $^1$H NMR ($CDCl_3$): $\delta$ 1.69 (d, J = 6.8 Hz, 3H, minor), 1.77 (d, J = 6.8 Hz, 3H, major), 4.08-4.24 (dq, 1H, major and minor), 6.03 (s, 1H, minor), 6.12 (s, 1H, major), 7.10-7.30 (m, 10H, major and minor); $^{13}$C-NMR ($CDCl_3$): $\delta$ 19.05 (q), 20.07 (q), 41.69 (d), 42.63 (d), 63.32 (d), 63.51 (d), 125.03 (d), 125.82 (d), 126.45 (d), 126.72 (d), 126.87 (d), 127.58 (d), 128.64 (d), 128.84 (d), 128.90 (d), 128.99 (d), 138.72 (s), 139.88 (s); Anal. Calcd for $C_{15}H_{15}NOS$: C, 71.35; H, 5.61; N, 5.20; S, 11.90. Found: C, 71.28; H, 5.73; N, 5.19; S, 11.92.

**2-tert-Butyl-5-methyl-3-phenyl-thiazolidin-4-one (2.14c)**
Aniline (2.79 g, 30 mmol), thiolactic acid (3.18 g, 30 mmol) and pivalaldehyde (80%) (3.23 g, 30 mmol) were refluxed azeotropically overnight in 100 ml pentane. The mixture was evaporated to dryness and redissolved in ether. The organic layer was washed with $NaHCO_3$-solution, 1N HCl and brine and dried ($Na_2SO_4$). After evaporation there remained crude **2.14c** (diastereomeric ratio 1:1), which was recrystallized from EtOH to give colourless needles (1.37 g, 5.5 mmol, 18%, diastereomeric ratio 1:4); mp 123.9-128.8 °C; $^1$H NMR ($CDCl_3$): $\delta$ 0.82 (s, 9H, major), 0.88 (s, 9H, minor), 1.53 (d, J = 7.0 Hz, 3H, minor), 1.67 (d, J = 7.2 Hz, 3H, major), 3.88-4.08 (dq, 1H, major and minor), 4.94 (s, 1H, minor), 5.12 (s, 1H, major), 7.24-7.42 (m, 5H, major and minor); $^{13}$C NMR ($CDCl_3$): $\delta$ 18.58 (q), 20.99 (q), 26.43 (q), 26.55 (q), 37.35 (s), 39.81 (s), 40.93 (d), 41.40 (d), 71,16 (d), 72.13 (d), 125.83 (d), 126.74 (d), 126.85 (d), 127.38 (d), 129.00 (d), 129.11 (d), 140.02 (s), 174.17 (s); Anal. Calcd for $C_{14}H_{19}NOS$: C, 67.43; H, 7.68; N, 5.62;

S, 12.87. Found: C, 67.32; H, 7.77; N, 5.55; S, 12.75.

**(2*S*,5*R*)-5-Methyl-3-phenyl-2-pyridin-2-yl-thiazolidin-4-one (*cis*-2.14d)**
(*R*)-Thiolactic acid (1.06 g, 10 mmol), aniline (0,93 g, 0.91 ml, 10 mmol) and 2-pyridinecarboxaldehyde (1.07 g, 0.95 ml, 10 mmol) were azeotropically refluxed overnight in 100 ml benzene in a Dean-Stark apparatus. The mixture was evaporated and crude **2.14d** was obtained (d.e. 91% as judged by 200 MHz $^1$H NMR). This material was recrystallized from EtOH to give diastereomerically pure *cis*-**2.14d** (1.84 g, 6.81 mmol, 68%); The *cis* conformation was established by NOEsy spectroscopy; mp 204.8-205.2 °C; From the mother liquor another 320 mg material could be obtained, which was a 1:1 mixture of diastereomers; $^1$H NMR ($CDCl_3$): $\delta$ 1.65 (d, J = 7.0 Hz, 3H), 4.31 (q, J = 7.0 Hz, 1H), 6.03 (s, 1H), 7.12-7.31 (m, 8H), 7.59-7.68 (m, 1H), 8.56 (d, J = 4.4 Hz, 1H); $^{13}$C NMR ($CDCl_3$): $\delta$ 18.22 (q), 41.28 (d), 63.95 (d), 120.08 (d), 123.21 (d), 124.52 (d), 126.61 (d), 129.03 (d), 137.15 (d), 149.97 (d), 159.31 (s); Anal. Calcd for $C_{15}H_{14}N_2OS$: C, 66.64; H, 5.22; N, 10.36; S, 11.86. Found: C, 66.64; H, 5.14; N, 10.21; S, 11.71.

**2-tert-Butyl-5-methyl-thiazolidin-4-one (2.14e)**
Thiolactic acid (2.66 ml, 30 mmol), pivalaldehyde (80%) (3.23 g, 30 mmol) and ammoniumcarbonate (1.58 g, 16.5 mmol) were refluxed azeotropically in benzene (150 ml) for 2h. Ether was added and the mixture was washed twice with 2N $NH_3$ and brine. After drying ($Na_2SO_4$) and evaporation there remained a white solid (3.74 g, 21.6 mmol, 72%, diastereomeric ratio 2.5:1) which was recrystallized from EtOH; mp 106.2-111.6 °C; $^1$H NMR ($CDCl_3$): $\delta$ 0.97 (s, 9H, major and minor), 1.59 (d, J = 7.1 Hz, 3H, minor), 1.60 (d, J = 7.0 Hz, 3H, major), 3.68-3.82 (dq, J = 7.1 Hz and J = 2.1 Hz, 1H, minor), 3.82 (q, J = 7.0 Hz, 1H, major), 7.93 (br, 1H, major and minor); $^{13}$C NMR ($CDCl_3$): $\delta$ 19.53 (q), 19.83 (q), 24.96 (q), 25.16 (q), 35.03 (s), 36.68 (s), 40.77 (d), 41.18 (d), 65.66 (d), 66.01 (d), 177.88 (s); Anal. Calcd for $C_8H_{15}NOS$: C, 55.45; H, 8.73; N, 8.08; S, 18.50. Found: C, 55.34; H, 8.78; N, 7.92; S, 18.40.

**2-Isopropyl-5-methyl-thiazolidin-4-one (2.14f)**
Thiolactic acid (3.18 g, 30 mmol), ammoniumcarbonate (1.59 g, 16.5 mmol) and isobutyraldehyde (2.16 g, 30 mmol) were azetropically refluxed for 5h in 100 ml benzene. The reaction mixture was washed with 1N $NH_3$ and brine. After drying ($Na_2SO_4$) and evaporation crude **2.14f** was obtained. This was recrystalized from EtOAc/hexane to yield diastereomerically pure **2.14f** (1.53 g, 9.7 mmol, 32%). Probably the moderate yield arises from the fact that the reaction was not complete after 5h and longer reaction times should be employed; $^1$H NMR ($CDCl_3$): $\delta$ 0.95-1.00 (dd, 6H), 1.50 (d, J = 7.1 Hz, 3H), 1.78-1.95 (m, 1H), 3.80 (q, J = 7.1 Hz, 1H), 4.53 (d, J = 5.7 Hz, 1H), 8.23 (br, 1H); $^{13}$C NMR ($CDCl_3$): $\delta$ 17.42 (q), 18.36 (q), 19.96 (q), 34.79 (d), 41.21 (d), 62.03 (d), 178.14 (s).

**3,5-Dimethyl-2-phenyl-thiazolidin-4-one (2.14g)**
This compound was prepared according to a literature procedure.[29a] A 4:1 mixture of diastereomers was obtained (literature 8:1).

**(*R*)-*N*-(2-methylpropane)-*N*-phenyl-2-mercaptopropane amine (2.15)**
In an atmosphere of nitrogen in dried glassware thiazolidinone (*R*)-**2.14a** (829 mg, 3.2 mmol, mixture of diastereomers) was dissolved in 25 ml of THF and borane.THF (1M, 6.5 ml) was added. The mixture was refluxed overnight and after cooling the reaction was quenched by cautious addition of 1N NaOH. The mixture was extracted three times with ether. The combined organic layers were washed with brine and dried ($Na_2SO_4$). After evaporation crude **2.15** was obtained, which was purified by bulb-to-bulb distillation to provide the pure title compound (558 mg, 2.5 mmol, 78%) as a colourless oil; $^1$H NMR ($CDCl_3$): $\delta$ 0.93 (d, J = 6.4 Hz, 6H), 1.33 (d, J = 6.0 Hz, 3H), 1.61 (d, 1H, J = 5.6 Hz), 2.11 (m, 1H), 3.11-3.55 (m, 5H), 6.67-6.74 (m, 3H), 7.20-7.29 (m, 2H); $^{13}$C NMR ($CDCl_3$): $\delta$ 20.38 (q), 22.05 (q), 26.33 (d), 32.90 (d), 60.64 (t), 61.94 (t), 112.87 (d), 116.23 (d), 129.19 (d), 147.43 (s); e.e. 89% ($MePOCl_2$-method[33] after 9 months).

**(2*S*,5*S*)-5-Benzyl-2-isopropyl-5-methyl-thiazolidin-4-one (2.16)**
Under an atmosphere of nitrogen in dried glassware diisopropylamine (167 mg, 0.23 ml, 1.65 mmol) was dissolved in 10 ml of THF. The mixture was cooled to -80°C and n-BuLi (1.6 N, 1.0 ml, 1.6 mmol) was added. After stirring for 15 min the mixture was recooled to -80°C and (2*S*,5*R*)-**2.14a** (352 mg, 1.5 mmol) was added dropwise in 10 ml of THF. The mixture was stirred for 15 min, recooled to -80°C and benzyl bromide (273 mg, 0.19 ml, 1.6 mmol) was added in THF. The mixture was stirred overnight during which it slowly reached room temperature. $NH_4Cl$ solution was added and the mixture was extracted three times with ether. The combined organic layers were washed with brine and dried ($Na_2SO_4$). After evaporation crude **2.16** was obtained. This was purified by column chromatography (silica, EtOAc/hexane 1:9) to give pure **2.16** (360 mg, 1.11 mmol, 81%) as a single diastereomer (>97% by 200 MHz $^1$H NMR); $^1$H NMR ($CDCl_3$): $\delta$ 0.73 (d, J = 5.2 Hz, 3H), 0.76 (d, J = 4.8 Hz, 3H), 1.69-1.77 (m, 1H), 1.76 (s, 3H), 2.85 (d, $J_{AB}$ = 13.1 Hz, 1H), 3.32 (d, $J_{AB}$ = 13.1 Hz, 1H), 4.19 (d, J = 3.2 Hz, 1H), 6.80-6.86 (m, 2H), 7.24-7.38 (m, 8H); $^{13}$C NMR ($CDCl_3$): $\delta$ 13.71 (q), 18.25 (q), 28.23 (d), 28.49 (q), 47.91 (t), 55.78 (s), 65.78 (s), 126.08 (d), 126.91 (d), 127.07 (d), 127.85 (d), 128.93 (d), 130.78 (d), 136.74 (s), 137.63 (s); HRMS m/z calcd 325.150. Found 325.150.

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28. See chapter 6, table 5.1 for the explanation of these abbreviations.

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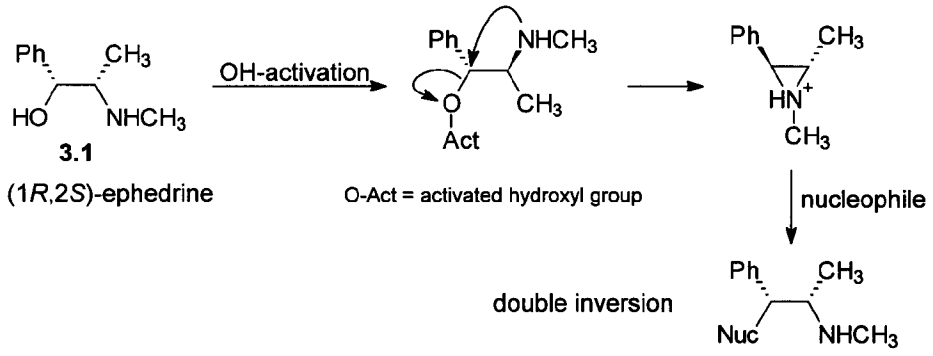
# Chapter 3

# Synthesis of mercapto analogs of ephedrine

## 3.1 Introduction

As was shown in the previous chapter we encountered several problems during the synthesis of tertiary β-amino thiols derived from (*R*)-thiolactic acid. Therefore, at the same time, we tried to find a way to convert readily accessible optically pure β-amino alcohols to the corresponding β-amino thiols. A PhD-student in our group, Martin Poelert, was working at that time to invert ephedrine (**3.1**) to pseudoephedrine (**3.2**). However, most of his efforts had been in vain because of rapid intramolecular nucleophilic attack by the nitrogen moiety, resulting in aziridine formation with *inversion* of configuration. Subsequent reaction using oxygen nucleophiles resulted in substitution with, again, *inversion* of configuration giving the product with net *retention* of configuration (scheme 3.1).[1]




*Scheme 3.1 Intramolecular aziridine formation of ephedrine upon attempted inversion reactions*

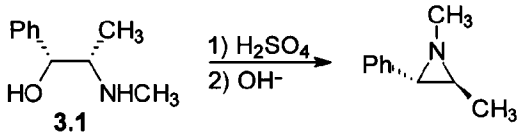
This double inversion reaction opens the way to make use of other nucleophiles than oxygen ones for substitution purposes. One could make use of, for example, phosphorous or nitrogen nucleophiles to convert ephedrine to β-amino phosphines and/or diamines. Since we were interested in the preparation of β-amino thiols as possible ligands, the use of several sulfur nucleophiles to obtain mercapto analogs of ephedrine was examined.

## 3.2 Aziridine formation of ephedra alkaloids

As stated, ephedrine gives rise to intramolecular aziridine formation upon activation

of the hydroxyl function. In principle it should be possible to isolate and purify such aziridines. The value of such optically pure aziridines is beyond doubt. Recently an extensive review has appeared dealing with the possible applications of chiral aziridines.[2]

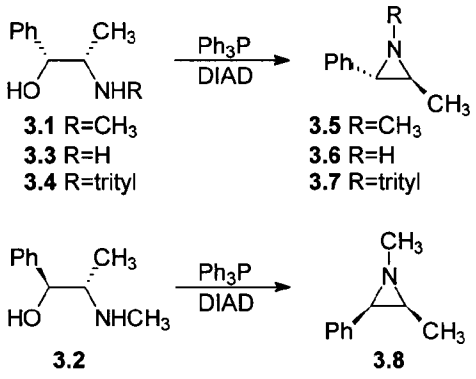
In the literature several procedures are known to convert β-amino alcohols to aziridines. The most classical one is the so called Wencker process in which first the *O*-sulfuric ester of the alcohol is produced by reaction with sulfuric acid, and subsequently, by action of strong base, the aziridine is formed (scheme 3.2). Production of aziridines derived from ephedra alkaloids using this methodology is claimed in literature,[3] but experimental details are lacking.




**3.1**

*Scheme 3.2 Aziridine formation via the Wencker process*

Another method consists of the use of triphenylphosphinedihalogenides (not illustrated); triphenylphosphine oxide and HBr are formed on ring closure. However, it was shown that only *cis*-aziridines derived from *threo*-β-amino alcohols could be produced.[4] The less stable *trans*-aziridine probably polymerizes[5] under the acidic conditions of the reaction. To produce the desired aziridines, we turned to a one-pot literature procedure[6] which converts β-amino alcohols to aziridines under Mitsunobu conditions.[7] Usually under Mitsunobu conditions it is difficult to purify the product due to large amounts of side-product, but because the aziridines formed are volatile, they can be isolated in satisfactory yields from the reaction mixture by distillation. Using this approach, aziridines from both *threo*- and *erythro*-




**3.1** R=$CH_3$
**3.3** R=H
**3.4** R=trityl

**3.5** R=$CH_3$
**3.6** R=H
**3.7** R=trityl

**3.2**

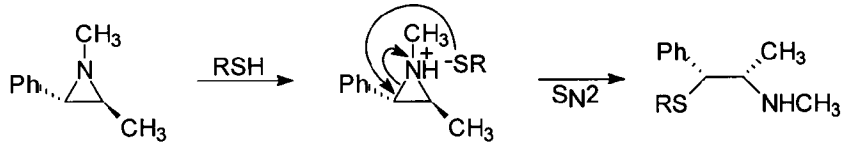
**3.8**

*Scheme 3.3 Aziridine formation of ephedra alkaloids via Mitsunobu reaction*

β-amino alcohols have been produced. In this way we prepared aziridines **3.5**, **3.6**, **3.7**, **3.8** from the corresponding ephedra alkaloids (scheme 3.3). The following sections will deal with the ring opening of these aziridines using several sulfur nucleophiles.

### 3.3 Ring opening of aziridines using sulfur nucleophiles

Unless symmetrically substituted, ring opening of aziridines can in principle take place on either of both carbon atoms. Usually aziridines are ring opened under acidic conditions unless strong nucleophiles are employed. It has been suggested that ring opening of aziridines can proceed through an $S_N1$ or $S_N2$ mechanism. The former takes places if tertiary carbon atoms are presents, whereas the latter route is followed for primary and secondary carbon atoms.[8] Studies of ring openings of aziridines in which both carbon atoms are secondary (as in our case) has revealed that usually inversion takes place on the reaction site. Also it is known that basic aziridines can be readily ring opened with sulfur nucleophiles including thiols, thiophenols, thiolacids and hydrogen sulfide. A general reaction pathway may be envisioned as in scheme 3.4. In the first stage the thiol protonates the basic aziridine generating an ion pair. Upon nucleophilic attack of the thiolate, the partial positive charge developed on the carbon atom in the transition state is best stabilized on the benzylic position, so reaction will mainly take place there.



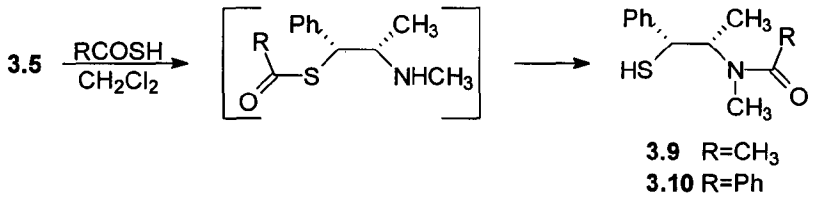

*Scheme 3.4 General mechanism of ringopening of basic aziridines with thiols*

This is indeed what is observed in most cases. Since thiolates are more nucleophilic than the amines formed, there is no other competing nucleophilic attack so the use of an excess of thiolate is not needed.

### 3.4 Ring opening of ephedra derived aziridines with thiolacids

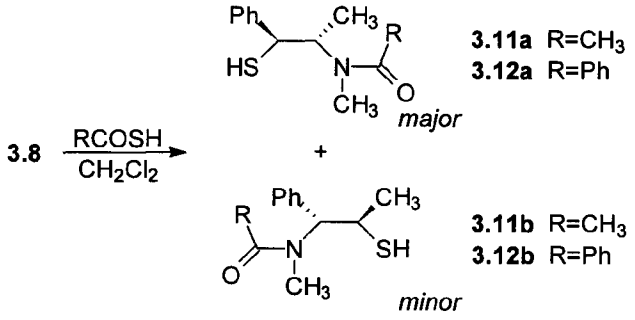
As is to be expected on the basis of the mechanism described in scheme 3.4, ring opening of *trans*-aziridine **3.5** with thiolacetic acid and thiolbenzoic acid should proceed very readily. Indeed this is the case. The reactions are exothermic and go to completion within minutes yielding the product as a single diastereomer. From the $^1$H-NMR spectra it was clear that not the expected thiolacetates or benzoates were produced, but that a rearrangement to the amides **3.9** and **3.10** had taken place (scheme 3.5). Such an acyl shift from sulfur to nitrogen has been observed

previously upon ring opening of aziridines with mercapto acids.[9]




*Scheme 3.5 Ringopening of aziridines by thiolacids followed by acyl shift*

Hindered rotation around the amide bond was observed and a clear coupling between the -SH and the benzylic proton was present as well, indicating a regioselective ring opening at the benzylic center. By increasing the temperature in DMSO-*d6* the doubled signals of compound **3.10** collapse to one at 130 °C. From the characteristic $J_{vic}$ coupling constants for the *erythro* (ephedrine, $J_{vic}$ = 2-7 Hz) and *threo* (pseudo-ephedrine, $J_{vic}$ = 7-10 Hz) series it was concluded that reaction had taken place with inversion of configuration at the benzylic center, and that the product belonged to the expected ephedra series, thus confirming structures **3.9** and **3.10**. Also *trans*-aziridine **3.6** was ring opened selectively with thiol acids under the same conditions. When, however, we turned to ring opening of the *cis*-aziridine **3.8** derived from pseudo-ephedrine, it was observed that a substantial amount (10-15%) of nucleophilic attack took place at the non-benzylic center leading to a mixture of products. The two isomers could fortunately be separated using column chromatography (scheme 3.6).



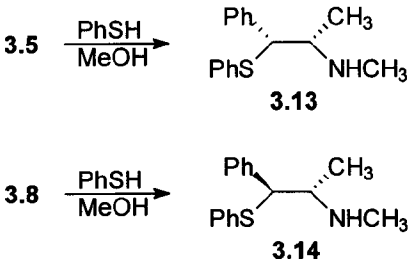

*Scheme 3.6 Non-selective ringopening of cis-aziridine **3.8***

A similar distribution of regioisomers was also observed in literature upon attack by $HN_3$.[10] When the reaction of **3.8** with thiolacetic acid was performed in diethyl ether in stead of $CH_2Cl_2$, the *major*-product **3.11a** crystallized from the reaction mixture as long white needles. In this way isomerically pure **3.11a** was readily

obtained.

### 3.5 Ring opening of ephedra derived aziridines with thiophenols

Thiophenols are also known to react with several aziridines.[11] Also in our case, thiophenol reacted smoothly with *trans*-aziridine **3.5** to give amino sulfide **3.13** in good yield. Again the reaction was completely site specific. However, when *cis*-aziridine **3.8** was treated with thiophenol under the same conditions it took several days for the reaction to go to completion. Elevation of temperature gave only rise to a small increase in reaction rate. Better results were obtained when more polar solvents like methanol were used.[12] Reaction then proceeded smoothly overnight. In contrast to ring opening using thiol acids, the ring opening now proceeded regioselectively on the benzylic center yielding **3.14** as a single isomer (scheme 3.7).



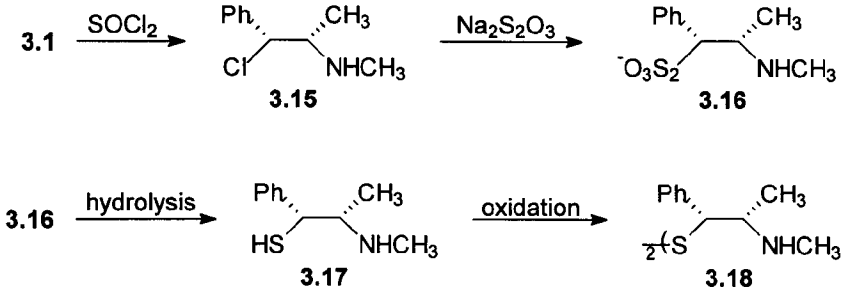

*Scheme 3.7 Ringopening of aziridines with thiophenol*

The compound, however, which we were most eager to prepare was thiolephedrine (**3.17**), in which the hydroxyl group has been substituted for a thiol group. This compound was expected to be most promising as a chiral ligand, since it has both an amine and a *free* thiol group in conjunction with its ephedra backbone.

### 3.6 Preparation of thiolephedrines

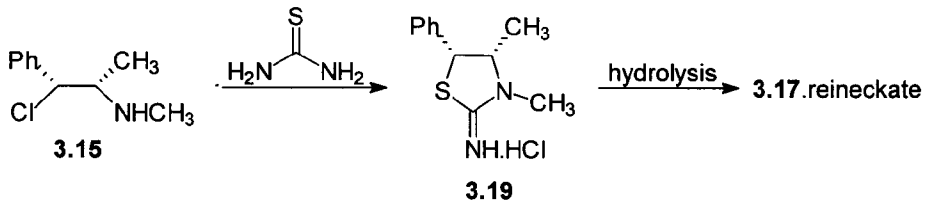
Thiolephedrine (**3.17**) it not an unknown compound in the literature. Several authors have claimed the preparation of **3.17** or the corresponding disulfide **3.18**, but the routes followed have the mutual disadvantage that yields are usually quite low and procedures are tedious. Some pharmacological studies on **3.17** and its disulfide **3.18** have also been undertaken.[13,14] One method to prepare **3.17** and analogs consists of converting ephedrine to the mercapto analog via Bunte-salt formation.[15] First ephedrine is converted with retention of configuration to the corresponding chloride **3.15** (via double inversion). This chloride is then converted into the Bunte salt **3.16** via reaction with $Na_2S_2O_3.5H_2O$. This reaction proceeds again with double inversion via the aziridinium ion, although some racemization

occurs during this reaction as well. Optically pure Bunte salt **3.16** is obtained after several crystallizations which significantly lowers the yield. The Bunte salt is subsequently hydrolysed in moderate yield to **3.17** which, due to its sensitivity to oxidation, is converted to the corresponding disulfide **3.18** (scheme 3.8). More recently the NMR-spectra of the disulfides and Bunte-salts have been published by Gelbcke.[16]




*Scheme 3.8 Synthesis of thiolephedrine disulfide (**3.18**) via the Bunte salt*

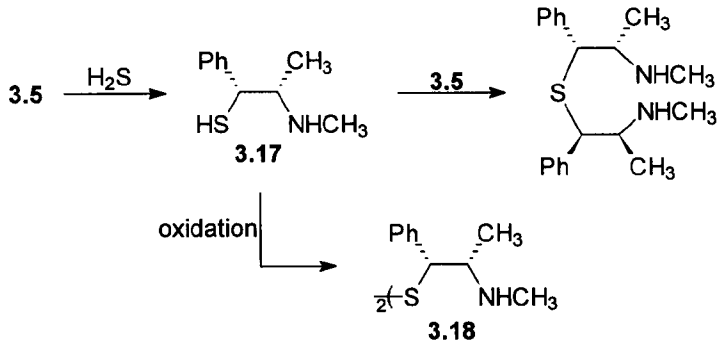
The amino thiol **3.17** is also prepared via action of thiourea on **3.15**. The iminothiazolidine **3.19** which is formed in 25% yield can be hydrolyzed to **3.17**.[17] The authors were only capable of isolating the product in the form of its reineckate (ammonium tetrathiocyanatodiaminechromate) (scheme 3.9).




*Scheme 3.9 Synthesis of thiolephedrine (**3.17**) using thiourea*

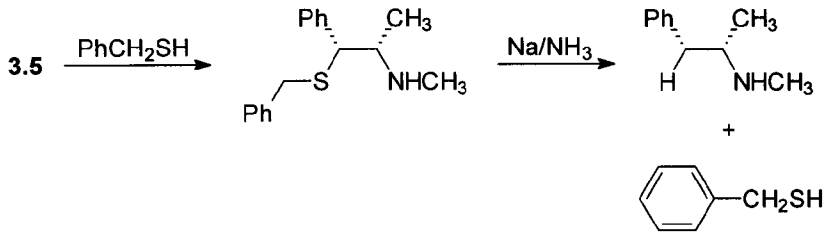
Some other attempts to prepare thio derivatives of the ephedra alkaloids via Bunte salts were undertaken by a Japanese company in the late 1950's, but unfortunately their work has only appeared in Japanese.[18] A more recent approach is the reaction of $H_2S$ with ephedrine in liquid HF. Under these rather drastic conditions **3.17**, contaminated with disulfide **3.18**, was formed in moderate (40%) yield.[19] It is therefore clear that the use of aziridines **3.5** and **3.8** might give drastic improvements in the synthesis of thiolephedrine and pseudo-thiolephedrine.
At first we tried whether aziridine **3.5** could be opened selectively with $H_2S$. This would in principle give rise to direct formation of **3.17**. Probably **3.17** is formed

under the reaction conditions, but **3.17** formed can either immediately react with another aziridine **3.5** to give the sulfide, or oxidize in the presence of air to the corresponding disulfide **3.18** (scheme 3.10). The ratio of sulfide vs. disulfide was strongly dependent on the solvent used. Best results were obtained in $CH_2Cl_2$ in which slow formation to the almost pure disulfide **3.18** took place. By adding the aziridine very slowly to a saturated solution of $H_2S$ in methanol sulfide formation could be suppressed as well, but completely selective production of only **3.18** was never observed.




*Scheme 3.10 Sulfide and disulfide formation upon ringopening of aziridine 3.5 with $H_2S$*

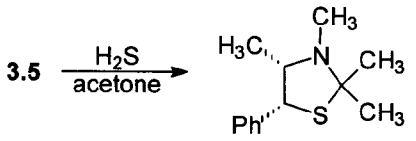
It proved to be impossible to separate the sulfide and disulfide by column chromatography. Formation of mixtures of sulfide and disulfide upon ring opening of ethylenimines by $H_2S$ has been reported more often in the literature.[20]




*Scheme 3.11 Ringopening of **3.5** by benzylmercaptam followed by reductive debenzylation*

Another possibility to produce **3.17** is the ring opening of **3.5** by benzyl mercaptan to yield *S*-benzyl-thiolephedrine, which subsequently can be debenzylated to yield **3.17** (scheme 3.11). Ring opening of **3.5** gave the desired product regioselectively, but subsequent reductive debenzylation proceeded at the *'wrong'* benzylic carbon-atom yielding deoxy-ephedrine and benzyl mercaptan.

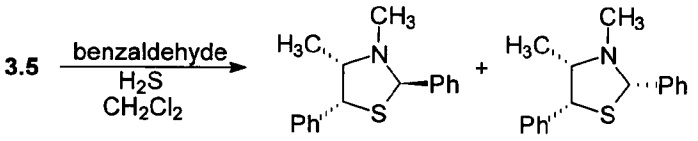
The solution to produce **3.17** from **3.5** is to perform the ring opening with $H_2S$ in the presence of a ketone or aldehyde. For example, when the reaction was performed in acetone as the solvent, product **3.17** is immediately trapped in the form of its *N,S*-acetal to give thiazolidine **3.20** (scheme 3.12). Such condensations are known to proceed in good yields.[21]




**3.20**

*Scheme 3.12 Thiazolidine formation from aziridine **3.5**, $H_2S$ and acetone*

A disadvantage of this reaction is the production of traces of thiolacetone by direct reaction of $H_2S$ and acetone. This compound has a very penetrating odour, which can be smelled miles away from the laboratory. It is therefore better to use another organic solvent, and just to add acetone as a reagent in small excess to suppress thiolacetone formation. Using this methodology also condensations using aldehydes, such as benzaldehyde, have been performed (scheme 3.13).




**3.21**

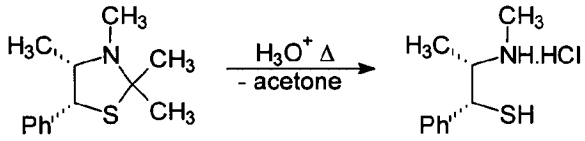
*Scheme 3.13 Formation of **3.21** by action of $H_2S$ and benzaldehyde on **3.5***

Upon reaction with an aldehyde a new chiral center is produced and the product is isolated as a mixture of diastereomers. Attempts to separate the diastereomers of **3.21** by either crystallisation or column chromatography failed. Although the diastereomers could be seen separately on TLC, isolation of pure fractions was impossible. Probably the diastereomers interconvert via an iminiumion, as is known for the reversible formation of oxazolidines from ephedrine and aromatic aldehydes.[22]

Unfortunately no reaction took place when we tried to ring open *cis*-aziridine **3.8** instead of **3.5**, using $H_2S$ and acetone in order to obtain a precursor for pseudo-thiolephedrine,

Although formation of **3.17** from the corresponding thiazolidines by acetal hydrolysis seems easy, it proved to be more difficult than expected. Under acidic or alkaline conditions only traces of **3.17** were produced. The main reason for this is that the hydrolysis is an equilibrium process. The equilibrium for our reaction

probably has a strong tendency towards the thiazolidine side, therefore preventing hydrolysis. This problem was solved by a suggestion from Prof. Martens who had encountered similar phenomena in his previous work.[23] By steam distillation under acidic conditions the acetone liberated from hydrolysis of **3.20** is azeotropically removed during the reaction, and the equilibrium is shifted to the product side (scheme 3.14).

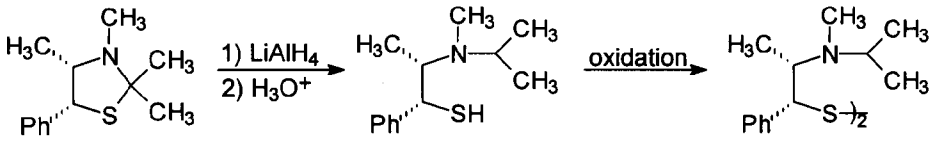



**3.20** **3.17**.HCl

*Scheme 3.14 Hydrolysis of thiazolidinine **3.20** to **3.17** by azeotropic acetone removal*

As already mentioned, amino-thiols have a tendency to oxidize rapidly to the disulfide. The rate of oxidation of thiols is generally promoted by bases; in this case intramolecular deprotonation by the amino group is the likely cause for the sensitivity to oxidation. It has been therefore impossible to isolate pure **3.17** as the free base. Although this oxidation can be excluded by working in a nitrogen atmosphere, during work up the compound is exposed to air and partly oxidizes to the disulfides. Using the reaction conditions described in scheme 3.14 the HCl-salt of **3.17** is produced after evaporation of excess of water. This salt is a stable, insensitive to oxidation, white solid. Upon trying to isolate **3.17** as free base by extraction under basic conditions a mixture of **3.17** and its disulfide **3.18** were isolated. By iodine catalyzed oxidation this mixture could be converted completely to **3.18**.

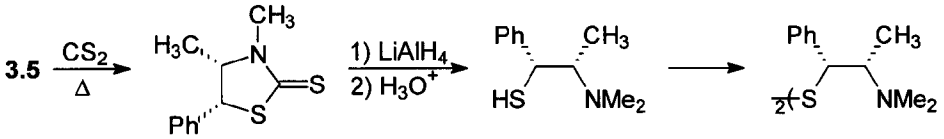
Another way to produce thiolephedrines from **3.20** is by reduction of the thiazolidine. In this way *N*-alkyl derivatives of thiolephedrine are produced such as *N*-isopropyl-thiolephedrine (**3.22**) (scheme 3.15). Several reducing agents were shown to be capable of performing the desired reduction of which $LiAlH_4$ was the best.




**3.20** **3.22** **3.23**

*Scheme 3.15 Reduction of thiazolidine **3.20** to N-isopropyl-thiolephedrine*

Probably some over-reduction occurs as well (as for the thiazolidinones, see chapter 2) to produce *N*-alkyl-deoxy-ephedrine as was judged from the NMR-data. Upon isolation, the produced amino-thiol again partially oxidizes to the disulfide. No attempts were undertaken to isolate these free thiols but the mixtures were immediately further oxidized to yield the corresponding disulfides as single product. Another sulfur reagent known to react with aziridines is $CS_2$,[24] the product being a thiazolidinethione (scheme 3.16). Indeed, freshly distilled **3.5** yielded thiazolidinethione **3.24** in 81% yield. It is important to use freshly distilled aziridine because of rapid polymerization of impure **3.5** at reflux temperatures. Just as for the reaction with $H_2S$, *cis*-aziridine **3.8** failed to give the desired reaction with $CS_2$.




**3.24** **3.25** **3.26**

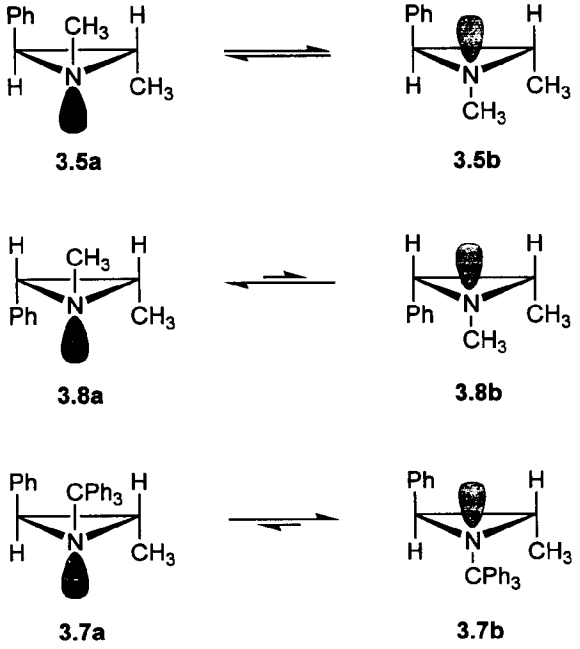
*Scheme 3.16 Synthesis of N-methyl-thiolephedrine via thiazolidinethione **3.24***

Under reductive conditions it was possible to convert thiazolidinethione **3.24** to *N*-methyl-thiolephedrine (**3.25**). Also this compound was oxidation sensitive and was isolated in the form of its disulfide **3.26**.

### 3.7 Reactivity of *cis*- and *trans*- aziridines derived from ephedra alkaloids

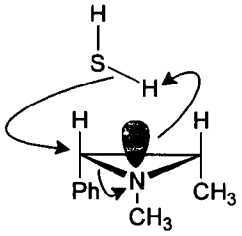
The remarkable difference in reactivity of *trans*-aziridine **3.5** compared to its *cis*-analog **3.8** is still not completely understood by us, but the conformation of both aziridines is probably very important. It is known that for unsymmetrical aziridines a different ratio of conformers **a** and **b** is possible.[25] These conformers can interchange by tunnelling of the nitrogen lone pair. For *trans*-aziridine **3.5** the energy difference for both conformers is not very different, but for *cis*-aziridine **3.8** the *N*-methyl is by preference positioned *trans* to the other substituents due to steric repulsion. The alternative all-*cis* conformation is energetically much less favoured. Semi-empirical calculations performed by Rob Zijlstra show indeed a

marginal difference in heat of formation for both conformers of **3.5**, but a larger difference for the conformers of **3.8**. This energy difference is big enough to conclude that **3.8** adopts conformation **3.8a** (scheme 3.17).[26] These calculations, however, only give an indication of the energy difference and more advanced *ab initio* calculations are needed to obtain more reliable results.




*Scheme 3.17 Different conformers of ephedra aziridines*

Upon using strong sulfur nucleophiles, such as thiol acids and thiophenols, both aziridines **3.5** and **3.8** can react due to the $S_N2$ character of the reaction. These acidic thiols can first form an ion pair with the aziridine and subsequently the thiolate can act as the nucleophile (scheme 3.4). Upon changing the sulfur nucleophiles to the less acidic $H_2S$ or $CS_2$, the reaction has to go through a less polarized intermediate to yield the desired product, since protonation of the aziridine is no longer possible. The reaction adopts more the features of a concerted cycloaddition. For such a reaction the geometry of the reactants in the transition state is very important. The aziridines have to adopt conformation **3.5a** or **3.8b** to position the nitrogen lone pair on the right position on the ring for reaction (scheme 3.18).



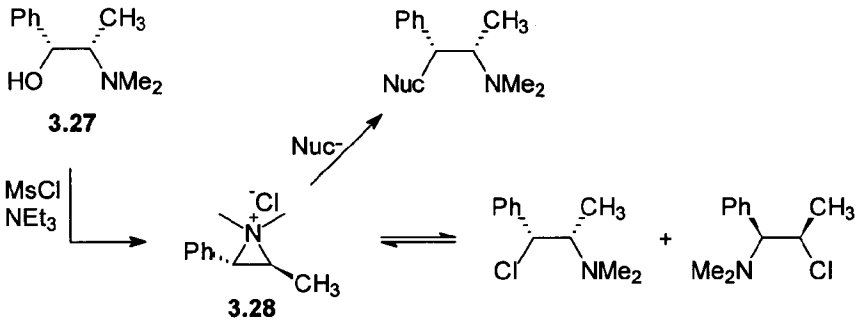

**3.8b**

*Scheme 3.18 Concerted reaction of aziridine **3.8** with $H_2S$*

This is possible for **3.5** but as **3.8** is merely in conformation a no reaction takes place. To test this postulate we prepared *N*-trityl-*trans*-aziridine **3.7** (scheme 3.3). For this aziridine conformation a would be less favoured due to the steric repulsion between the large trityl and the phenyl group which arises upon *cis*-positioning of these groups (scheme 3.17). However, this is the conformation that is needed for reaction. What we indeed observed was that reaction of **3.7** with $H_2S$ and $CS_2$ was completely blocked, even at elevated temperatures and high pressures, thus giving an extra indication for our proposed conformational effect.

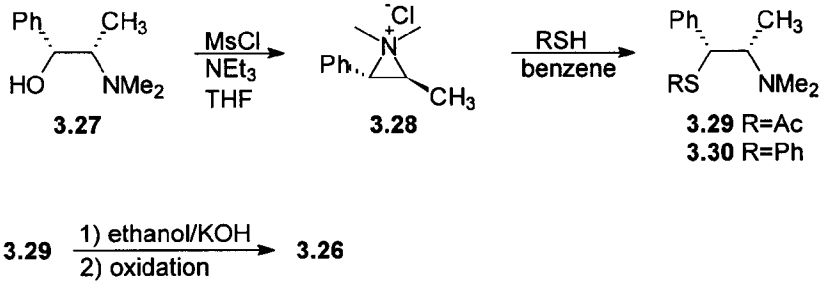
### 3.8 Alternative thiolephedra synthesis

Just before we submitted our manuscript on the synthesis of thiolephedrines[27] a very elegant paper from Dieter and Dieter appeared, describing the stereoselective synthesis of *N*-methylephedrine and pseudoephedrine derivatives via nucleophilic ring opening of an aziridinium ion **3.28**.[28] Thiolacetic acid was one of the nucleophiles tested. The method consists of reaction of *N*-methylephedrine with mesylchloride to yield an intermediate aziridinium ion. According to Dieter this ion can in principle give rise to the formation of two chloroamines, but due to its relative stability (compared to the pseudo-series) it will react by preference with other strong nucleophiles (scheme 3.19).
The observation by Dieter that upon reaction of *N*-methylephedrine with MsCl and subsequent aqueous work-up only starting material was recovered had already been observed by us previously. On that occasion we, however, by error, argued that the mesylate was extremely sensitive to hydrolysis.
We tested the methodology of Dieter by letting the intermediate aziridinium ion **3.28** of *N*-methylephedrine react with thiolacetic acid and thiophenol. It is essential that the crude **3.28**, prepared in THF, is redissolved in an apolar solvent like benzene before ring opening to ensure complete regioselectivity. A direct ring opening in THF (without work-up of **3.28**) gave complete ring opening, but approximately a 9:1 ratio of regioisomers was obtained. As can be seen in scheme




*Scheme 3.19 Substitution of N-alkyl-ephedrines via the aziridinium ion according to Dieter and Dieter*

3.20, both ring opening using thiolacetic acid and thiophenol proceeded regioselectively in benzene to yield **3.29** and **3.30**.
Either in alkaline ethanol or by using $LiAlH_4$ thiolacetate **3.29** could be converted to *N*-methyl-thiolephedrine **3.26**. The practical ease of this reaction and the avoidance of an uneconomical Mitsunobu step makes this procedure superior to ours for the preparation of *N*-methylthiolephedrines. Following the same strategy **3.23** could be prepared from *N*-isopropylephedrine. There is no reason to assume that this methodology cannot be extended to other *N*-alkylephedrines and *β-N,N*-bisalkylamino alcohols giving the possibility of making a large scala of chiral *β-N,N,*-bisalkylamino thiols. For the preparation of primary and secondary amino thiols and sulfides (such as thiolephedrine it self) our methodology, however, is still the most versatile.




*Scheme 3.20 Synthesis of thiolephedrine derivatives via the Dieter and Dieter procedure*

## 3.9 Conclusions

In this chapter we have shown that aziridines, directly derived from the optically pure ephedra alkaloids, can be selectively ringopened by a variety of sulfur nucleophiles. In this way a range of usefull optically pure β-amino thiols, -sulfides and -disulfides have been prepared. Using this procedure an improved way to prepare thiolephedrine **3.17** and some analogs has been found. To prepare *N*-alkyl derivatives of thiolephedrines, the Dieter and Dieter procedure was found to be superior. Also some remarkable differences in reactivity between *cis*- and *trans*-aziridines were observed. This is probably due to the existence of different ratios of conformers for the different aziridines. This arguement was further supported by the fact that *N*-trityl aziridine **3.7** failed to give reaction with $H_2S$ as well.

**Acknowledgement**: The pleasant cooperation with Martin Poelert to come to the results described in this chapter is greatfully acknowledged. Also Nathalie Peper is thanked for her synthetic efforts in the preparation of some of the compounds described in this chapter. Rob Zijlstra is acknowledged for the informative semi-empirical calculations performed on the aziridines.

## 3.10 Experimental

For general remarks see chapter 2.

**(1*R*,2*S*)-2-(Methyl-trityl-amino)-1-phenylpropan-1-ol (3.4)**
To a solution of (1*R*,2*S*)-norephedrine (**3.3**) (2.75 g, 18.2 mmol) and $Et_3N$ (1.84 g, 18.2 mmol) in $CH_2Cl_2$ (50 ml) was added trityl chloride (5.07 g, 18.2 mmol). After stirring overnight, water was added and the product was extracted with $CH_2Cl_2$. After drying ($MgSO_4$) and evaporation of the solvent **3.4** was obtained as a white solid (5.94 g, 15.1 mmol, 83%). Crystallisation from hexane gave white crystals; $[\alpha]_D^{25}$ + 77.6° (c, 1.0 in $CH_2Cl_2$); mp 118.0-118.1 °C; $^1$H-NMR ($CDCl_3$): $\delta$ 0.68 (d, J = 6.7 Hz, 3H), 2.12 (br, 1H), 2.72 (br, 1H), 3.00 (dq, J = 3.1 and 6.6 Hz, 1H), 3.91 (d, J = 3.0 Hz, 1H), 7.0-7.4 (m, 15H), 7.6-7.7 (m, 5H); $^{13}$C NMR ($CDCl_3$): $\delta$ 15.17 (q), 53.91 (d), 71.53 (s), 125.51 (d), 126.61 (d), 127.95 (d), 128.84 (d), 142.14 (s), 146.58 (s); HRMS m/z calcd 393.209. Found: no parent peak was found, the tritylfragment (m/z: 243.12) was the parent peak; Anal. Calcd for $C_{28}H_{27}NO$: C, 85.45; H, 6.92; N, 3.56. Found: C, 85.39; H, 6.90; N, 3.57.

**(2*S*,3*S*)-1,2-Dimethyl-3-phenylaziridine (3.5)**
This compound was prepared from (1*R*,2*S*) ephedrine (**3.1**) by a literature procedure.[6] *trans*-Aziridine **3.5** was isolated (81% yield) as a clear oil after bulb-to-bulb distillation (bath temperature; 75 °C, 1.0 mm Hg); $[\alpha]_D^{25}$ = + 83.2° (c, 1.18 in $CH_2Cl_2$); (lit.,[6] $[\alpha]_D^{25}$ = + 51.8° (no concentration or solvent reported)); $^1$H NMR

($CDCl_3$): $\delta$ 1.33 (d, J = 5.3 Hz, 3H), 2.0-2.1 (m, 2H), 2.52 (s, 3H), 7.2-7.3 (s, 5H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 10.42 (q), 37.92 (q), 42.19 (d), 49.17 (d), 125.43 (d), 126.23 (d), 127.81 (d), 129.81 (d), 140.33 (s); HRMS calcd m/z 147.104. Found 147.105.

**(2*S*,3*S*)-2-Methyl-3-phenylaziridine (3.6)**
This compound was synthesized in analogy with **3.5**. As the reaction was much slower a reaction time of 3 days was required. Starting from (1*R*,2*S*)-norephedrine (**3.3**) the product was isolated in 83% yield after bulb-to-bulb distillation (100 °C, 0.6 mm Hg) as a clear oil; $^1H$ NMR ($CDCl_3$): $\delta$ 1.26 (br, 1H), 1.26 (d, J = 5.5 Hz, 3H), 2.12 (br s, 1H), 2.65 (d, J = 2.7 Hz, 1H), 7.1-7.4 (m, 5H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 19.58 (q), 37.06 (d), 40.44 (d), 125.51 (d), 126.93 (d), 128.43 (d), 140.40 (s); HRMS m/z calcd 133.089. Found 133.089.

**(2*S*,3*S*)-2-Methyl-3-phenyl-1-tritylaziridine (3.7)**
This compound was synthezised in analogy with **3.5**. Starting from *N*-tritylephedrine (**3.4**) the product was obtained as a white foam in 82% yield after column chromatography (alumina, hexane/ether 4:1); $[\alpha]_D^{25}$ = + 7.5° (c, 0.52 in $CH_2Cl_2$); mp 94.6-97.8 °C; $^1H$ NMR ($CDCl_3$): $\delta$ 1.08 (d, J = 5.9 Hz, 3H), 2.78 (m, 2H), 7.2-7.4 (m, 15H), 7.6-7.7 (m, 5H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 14.52 (q), 42.61 (d), 44.31 (d), 73.13 (s), 126.19 (d), 126.63 (d), 126.65 (d), 126.78 (d), 127.32 (d), 128.14 (d), 129.91 (d), 140.87 (s), 146.19 (s). HRMS m/z calcd 375.199. Found 375.199.

**(2*S*,3*R*)-1,2-Dimethyl-3-phenylaziridine (3.8)**
This compound was prepared from (1*S*,2*S*)-pseudoephedrine (**3.2**) in the same way as **3.5**. Starting from **3.2** the product was obtained (85% yield) as a clear oil after bulb-to-bulb distillation (50 °C, 0.9 mm Hg); $[\alpha]_D^{25}$ = + 131.0° (c, 0.80 in EtOH); $^1H$ NMR ($CDCl_3$): $\delta$ 0.90 (d, J = 5.7 Hz, 3H), 1.66 (m, 1H), 2.42 (d, J = 7.2 Hz), 2.48 (s, 3H), 7.26 (s, 5H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 12.54 (q), 42.82 (q), 47.40 (d), 47.49 (d), 126.20 (d), 126.33 (d), 127.58 (d), 127.73 (d), 137.37 (s); HRMS calcd m/z 147.104. Found 147.105.

**(1*R*,2*S*)-2-(*N*-Methyl-acetamido)-1-phenylpropane-1-thiol (3.9)**
*trans*-Aziridine **3.5** (0.70 g, 4.76 mmol) was dissolved in 20 ml of $CH_2Cl_2$ and cooled to 0 °C. Thiolacetic acid (0.38 g, 5.00 mmol) was added and the reaction mixture was stirred under nitrogen. After 2 h more $CH_2Cl_2$ was added and the organic layer was washed with saturated $NaHCO_3$ solution (2 x 35 ml). After drying ($MgSO_4$) and evaporation of the solvent the crude product was subjected to column chromatography (silica, ether) and **3.9** was obtained (860 mg, 3.86 mmol, 81% yield) as a viscous oil; $[\alpha]_D^{25}$ = - 91.0° (c, 2.1 in $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$): $\delta$ 1.38 and 1.47 (d, J = 6.7 Hz and J = 6.4 Hz, 3H), 1.75 and 1.84 (s, 3H), 1.88 and 1.97 (d, J = 6.9 Hz and J = 5.2 Hz, 1H), 2.61 and 2.67 (s, 3H),

4.03 (m, 1H), 4.14 and 5.03 (m, 1H), 7.2-7.3 (m, 5H); $^{13}$C NMR ($CDCl_3$): $\delta$ 15.77 (q), 22.01 (q), 47.70 (q), 54.71 (d), 59,94 (d), 126.90 (d), 127.45 (d), 127.98 (d), 128.46 (d), 128.78 (d), 142.26 (s); according to GC this material had a purity of over 98%.

**(1*R*,2*S*)-2-(*N*-Methyl-benzamido)-1-phenylpropane-1-thiol (3.10)**
This compound was prepared in the same way as **3.9** using thiolbenzoic acid in stead of thiolacetic acid. Starting from **3.5**, **3.10** was obtained in pure form (88% yield) after column chromatography (silica, ether) as a white solid; mp 89.8-90.3 °C; $[\alpha]_D^{25}$ = - 64.9° (c, 1.74 in $CH_2Cl_2$); $^1$H NMR ($CDCl_3$): $\delta$ 1.49 (d, J = 6.8 Hz, 3H), 1.92 (d, J = 6.8 Hz, 1H), 1.47 and 2.78 (s, 3H), 4.01 (m, 1H), 4.18 and 5.10 (m, 1H), 6.63 (d, J = 6.4 Hz, 1H) 6.8-7.4 (m, 9H); $^{13}$C NMR ($CDCl_3$): $\delta$ 15.73 (q), 32.25 (q), 47.45 (d), 55.12 (d), 126.20 (d), 126.80 (d), 127.04 (d), 127.06 (d) 127.13 (d), 127.51 (d), 128.17 (d), 129,13 (d), 136.68 (s), 142.38 (s); No exact mass could be determined, due to ß-elimination of hydrogen sulfide. This was confirmed by the m/z 251 (285-34) peak in the mass spectrum; The purity of this material was over 99% according to GC.

**(1*S*,2*S*)-2-(*N*-Methyl-acetamido)-1-phenylpropane-1-thiol (3.11a)**
This compound was synthesized in the same way as **3.9**. Starting from *cis*-aziridine **3.8** (0.75 g, 5.1 mmol), **3.11a** was obtained (0.80 g, 3.6 mmol, 70%) as a white solid after chromatography (silica, ethyl acetate/hexane 1:2); mp 108-110 °C (decomp.) (lit.,[14] 112-113 °C); $^1$H NMR ($CDCl_3$): $\delta$ 0.85 and 0.91 (d, J = 6.8 Hz and J = 6.4 Hz, 3H), 1.83 and 1.86 (d, J = 5.6 Hz and J = 1.6 Hz, 1H), 2.07 and 2.23 (s, 3H), 2.77 and 2.83 (s, 3H), 3.91 and 4.97 (br s, 1H), 4.06 (m, 1H), 7.2-7.3 (m, 5H); $^{13}$C NMR ($CDCl_3$): $\delta$ 15.70 (q), 16.68 (q), 22.40 (q), 47.54 (d), 48.27 (d), 59.67 (d), 127.52 (d), 127.60 (d), 128.00 (d), 128.69 (d), 128.71 (d), 128.98 (d), 129.00 (d), 140.65 (s), 142.12 (s).
The other regioisomer **3.11b** was obtained (12%) as a white almost pure semisolid. $^1$H NMR ($CDCl_3$): $\delta$ 1.25 and 1.32 (d, J = 6.6 Hz and J = 6.6 Hz, 3H), 1.62 and 1.74 (d, J = 7.7 Hz and J = 4.1 Hz, 1H), 2.09 and 2.40 (s, 3H), 2.74 and 2.79 (s, 3H), 3.61 and 3.82 (m, 1H), 4.62 and 5.66 (d, J = 10.8 Hz and J = 11.1 Hz, 1H), 7.2-7.4 (m, 5H); $^{13}$C NMR ($CDCl_3$): $\delta$ 21.67 (q), 22.30 (q), 23.71 (q), 35.07 (q), 35.67 (q), 62.73 (d), 69.12 (d), 127.66 (d), 128.34 (d), 128.65 (d), 128.93 (d), 136.70 (s), 137.69 (s).
When the reaction was performed in 5 ml ether in stead of $CH_2Cl_2$ **3.11a** crystallized by preference from the reaction mixture and could be isolated by filtration.

**(1*S*,2*S*)-2-(*N*-Methyl-benzamido)-1-phenylpropane-1-thiol (3.12a)**
This compound was synthesized in the same way as compound **3.9** using thiolbenzoic acid in stead of thiolacetic acid. From *cis*-aziridine **3.8** (0.70 g, 5.1 mmol), the main product **3.12a** was obtained (1.09 g, 3.8 mmol, 82%) as a white

solid, after purification by column chromatography (silica, hexane/ethyl acetate 2:1), mp 95.7-96.2 °C; $[\alpha]_D^{25}$ = + 154.8° (c, 1.50 in $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$): $\delta$ 0.99 and 1.08 (d, J = 6.0 Hz and J = 6.8 Hz, 3H), 1.92 and 2.06 (d, J = 4.1 and J = 5.7 Hz, 1H), 2.90 and 3.07 (s, 3H), 4.16 (m, 1H), 4.1 and 5.1 (br, 1H), 7.0-7.6 (m, 10H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 15.58 (q), 15.68 (q), 16.76 (q), 16.84 (q), 26.45 (q), 47.69 (d), 48.55 (d), 59.95 (d), 126.97 (d), 127.35 (d), 127.67 (d), 127.90 (d), 128.43 (d), 128.55 (d), 128.93 (d), 129.34 (d), 129.48 (d), 141.06 (s), 142.33 (s), 172.12 (s); Anal. Calcd for $C_{16}H_{19}NOS$: C, 71.54; H, 6.71. Found: C, 71.01; H, 6.61. The other regioisomer was obtained in about 10% yield although not completely pure as was clear from the $^1H$ NMR spectrum.

**(1*R*,2*S*)-2-Methylamino-1-phenyl-1-phenylthio-propane (3.13)**
To a solution of *trans*-aziridine **3.5** (0.50 g, 3.4 mmol) in 5 ml of methanol was added at room temperature a slight excess of thiophenol (0.41 g, 3.7 mmol). The solution was allowed to stand overnight in a stoppered bottle. The solvent and the excess thiophenol were removed under reduced pressure. The product was further purified by eluting over a short pad of alumina with ether. A slightly yellow oil (0.69 g, 87% yield) was obtained; $[\alpha]_D^{25}$ = - 19.1° (c, 1.99 in $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$): $\delta$ 1.16 (d, J = 6.5 Hz), 1.54 (br, 1H), 2.40 (s, 3H), 2.99 (m, 1H), 4.33 (d, J = 5.8 Hz, 1H), 7.1-7.4 (m, 10H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 16.99 (q), 33.78 (q), 59.21 (d), 126.47 (d), 127.02 (d), 128.23 (d), 128.51 (d), 131.13 (d), 135.27 (s), 139.97 (s); Anal. Calcd for $C_{16}H_{19}NS$: C, 74.66; H, 7.44. Found: C, 73.95; H, 7.33.

**(1*S*,2*S*)-2-Methylamino-1-phenyl-1-phenylthio-propane (3.14)**
This compound was synthesized and purified in the same way as **3.13** starting from *cis*-aziridine **3.8**. The product was obtained (73% yield) as a colourless oil; $[\alpha]_D^{25}$ = + 253.1° (c, 1.60 in $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$): $\delta$ 1.00 (d, J = 6.4 Hz, 3H), 1.8 (br, 1H), 2.49 (s, 3H), 2.95-3.08 (m, 1H), 4.17 (d, J = 7.9 Hz, 1H), 7.0-7.3 (m, 10H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 17.51 (q), 33.80 (q), 58.69 (d), 59.92 (d), 126.91 (d), 127.13 (d), 128.21 (d), 128.27 (d) 128.56 (d) 128.68 (d), 131.95 (d), 134.93 (s), 140.24 (s); Anal. Calcd for $C_{16}H_{19}NS$: C, 74.66; H, 7.44. Found: C, 73.64; H, 7.30.

**(4*S*,5*R*)-2,2,3,4-Tetramethyl-5-phenyl-1,3-thiazolidine (3.20)**
*trans*-Aziridine **3.5** (0.59 g, 4.0 mmol) was dissolved in 5 ml of dry acetone and $H_2S$ was gently bubbled through for 15 min. The saturated solution was left standing overnight in a stoppered bottle. After evaporation of the solvent the remaining oil was subjected to column chromatography (silica gel, ether/hexane 1:15) to yield **3.20** as a white solid (0.76 g, 3.4 mmol, 86% yield); $[\alpha]_D^{25}$ = + 143.8° (c, 0.91 in $CH_2Cl_2$); mp 70-72 °C; $^1H$ NMR ($CDCl_3$): $\delta$ 0.81 (d, J = 6.4 Hz, 3H), 1.46 (s, 3H), 1.73 (s, 3H), 2.25 (s, 3H) 3.36 (m, 1H), 4.27 (d, J = 6.0 Hz, 1H), 7.2-7.5 (m, 5H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 17.26 (q), 24.02 (q), 29.64 (q),

32.24 (q), 53.25 (d), 63.69 (d), 126.78 (d), 127.64 (d), 129.57 (d), 142.26 (d). Anal. Calcd for $C_{13}H_{19}NS$: C, 70.54; H, 8.65; N, 6.27; S, 14.46. Found: C, 70.08; H, 8.66; N, 6.27; S, 14.46. HRMS calcd m/z 221.124. Found 221.124.

**(4*S*,5*R*)-3,4-Dimethyl-2,5-diphenyl-1,3-thiazolidine (3.21)**
*trans*-Aziridine **3.5** (2.90 g, 19.7 mmol) was dissolved in 5 ml of $CH_2Cl_2$. Benzaldehyde (3 ml, 29.6 mmol) was added and $H_2S$ was gently bubbled through for 15 min. After 3 days conversion was complete and excess solvent was evaporated. The remaining red-brown foam was purified by column chromatography (silica, ether/hexane 1:20) to yield **3.21** (1.80 g, 16.1 mmol, 82%) as a mixture of epimeres; mp 66.5-72.5 °C; $^1$H NMR ($CDCl_3$): $\delta$ 0.90 (d, J = 6.4 Hz, 3H), 2.17 (s, 3H), 2.26 (s, 3H), 2.94 (m, 1H), 3.82 (m, 1H), 4.42 (d, J = 6.4 Hz, 1H), 4.59 (s, 1H), 5.18 (s, 1H), (5.25 (d, J = 5.3 Hz, 1H), 7.2-7.6 (m, 10H); $^{13}$C NMR ($CDCl_3$): $\delta$ 16.93 (q), 18.93 (q), 37.62 (q), 37.69 (q), 54.34 (d), 55.67 (d), 67.71 (d), 67.85 (d), 71.84 (d), 75.40 (d), 127.04 (d), 127.82 (d), 128.24 (d), 128.59 (d), 129.79 (d), 139.90 (s), 142.00 (s); Anal. Calcd for $C_{17}H_{19}NS$: C, 75.80; H, 7.12; N, 5.20. Found: C, 75.43, H, 6.85, N, 5.07. HRMS calcd m/z 269.124. Found 269.124.

**(1*R*,2*S*)-2-Methylamino-1-phenylpropane-1-thiol.HCl (thiolephedrine.HCl) (3.17)**
Hydrolysis of **3.20** (0.60 g, 2.71 mmol) was performed by dissolving this compound in a large volume of 2N aqueous HCl (200 ml) and distilling off the liberated acetone by steam distillation. Evaporating of water gives near quantitatively thiolephedrine (**3.17**) in the form of its HCl salt. Recrystallization from EtOH (96%) gave analytically pure material (0.33 g, (1.92 mmol), 71%); mp 198.5-201.2 °C (dec.); $^1$H NMR ($D_2O$): $\delta$ 1.37 (d, J = 6.6 Hz, 3H), 2.74 (s, 3H), 3.73 (m, 1H), 4.46 (d, J = 6.5 Hz, 1H), 7.45 (m, 5H); $^{13}$C NMR ($D_2O$): $\delta$ 28.24 (q), 46.93 (q), 61.54 (d), 76.86 (d), 144.25 (d), 145.05 (d), 145.69 (d), 154.63 (s); Anal. Calcd for $C_{10}H_{16}ClNS$: C, 55.16; H, 7.41; N, 6.43; S, 14.72. Found: C, 55.16; H, 7.41; N, 6.68; S, 14.39.

**Bis-((1*R*,2*S*)-2-methylamino-1-phenylpropane-1-)-disulfide (3.18)**
Compound **3.17**.HCl was dissolved in 2N aqueous NaOH. The water layer was extracted 3 times with $CH_2Cl_2$ and the combined organic layers were dried ($Na_2SO_4$). The solvent was removed to give a mixture of **3.17** and **3.18**. This was dissolved in MeOH and air was bubbled through for 1 h. After evaporation crude **3.18** was obtained. For purification purposes this was converted to its bis HCl salt, **3.18**.2HCl which was recrystallized from EtOH (96%); mp 236.3-237.1 °C (decomp.) (lit,[15] 232 °C); $^1$H NMR ($D_2O$): $\delta$ 1.41 (d, J = 6.4 Hz, 6H), 2.63 (s, 6H), 3.66 (d, J = 8.1 Hz, 2H), 3.78 (m, 2H), 7.3 (m, 4H), 7.5 (m, 6H); $^{13}$C NMR ($D_2O$): $\delta$ 29.92 (q), 46.67 (q), 73.52 (d), 73.62 (d), 145.31 (d), 145.97 (d), 151.34 (s); Elemental analysis indicated the presence of one molecule of crystal water. Anal. Calcd for $C_{20}H_{30}Cl_2N_2S_2.H_2O$: C, 53.20; H, 7.14; N, 6.20; S, 14.20.

Found: C, 53.15; H, 7.12; N, 6.35; S, 13.87.

**Bis-((1*R*,2*S*)-2-(isopropyl-methyl-amino)-1-phenylpropane-1-)-disulfide (3.23)**
To a suspension of $LiAlH_4$ (152 mg, 4.0 mmol) in 50 ml of dry ether was added dropwise a solution of thiazolidine **3.20** (884 mg, 4.0 mmol) in dry ether. The mixture was refluxed for 4 h and quenched carefully with water. After filtration over celite and extensive washing of the salts with ether the combined organic layers were washed with brine, dried ($Na_2SO_4$) and evaporated to yield a mixture of thiol **3.22** and disulfide **3.23**. This mixture was dissolved in MeOH and a small $I_2$ crystal was added. Air was bubbled through for 2h and after evaporation of the solvent crude **3.23** was obtained. This was subjected to column chromatography (silica). Traces starting material and some impurities were washed of by elution with $CH_2Cl_2$ after which the product (620 mg, 1.4 mmol, 70%) was obtained by elution with MeOH; The product prepared this way was contaminated with about 10% of an impurity of unknown composition. Pure material was obtained *via* the Dieter and Dieter approach; $^1$H-NMR ($CDCl_3$): $\delta$ 0.83 (d, J = 6.6 Hz, 6H), 0.89 (d, J = 6.6 Hz, 6H), 1.18 (d, J = 6.3 Hz, 6H), 1.93 (s, 6H), 2.73 (m, 2H), 3.28 (m, 4H), 7.1-7.3 (m, 10H); $^{13}$C NMR ($CDCl_3$); $\delta$ 14.47 (q), 19.74 (q), 20.31 (q), 30.15 (q), 52.97 (d), 59.06 (d), 61.37 (d), 126.91 (d), 127.38 (d), 127.48 (d), 127.76 (d), 128.65 (d), 129.22 (d), 129.51 (d), 141.60 (s).

**(4*S*,5*R*)-3,4-Dimethyl-5-phenylthiazolidine-2-thione (3.24)**
To a solution of freshly distilled **3.5** (0.20 g, 1.36 mmol) in 5 ml of carbon tetrachloride was added at room temperature an excess of carbon disulfide (3 ml). The solution was gently refluxed for 12 h. Evaporation of the solvent and the excess carbon disulfide yielded **3.24** quantitatively as a yellow oil, which crystallized on standing. The solid material was recrystallized from diethyl ether/hexane 1:2 yielding (246 mg, 1.10 mmol, 81%) white needles; $[\alpha]_D^{25}$ = -153.0° (c, 0.52 in EtOH); mp 68.0-68.1 °C; (lit.,[14] 65-66 °C; $[\alpha]_D^{25}$ = -155° (c, 1 in EtOH)).

**Bis-((1*R*,2*S*)-2-dimethylamino-1-phenylpropane-1-)-disulfide (*N*-methylthiolephedrine disulfide) (3.26) from 3.24**
Compound **3.24** (0.50 g, 2.24 mmol) was reduced with $LiAlH_4$ (0.30 g, 7.91 mmol) according to a literature procedure.[14] Instead of ether 50 ml dry THF was used. Glauber salt ($Na_2SO_4.10H_2O$) was used for the work-up of this reaction. After quick filtration over Celite the solvent was removed in vacuo. Despite the precautions 5-10% of the disulfide was formed as indicated by the 60 Mhz $^1$H NMR spectrum. All of the crude material was dissolved in 20 ml ethanol and a stream of air was bubbled through this solution for 1 h. After evaporation of the solvent the disulfde **3.26** was isolated (0.24 g, 54% yield) as a white solid; no trace of the free thiol was found; mp 196.4-197.4 °C (decomp.); (lit.,[14] mp 196-197 °C). $^1$H NMR ($CDCl_3$): $\delta$ 0.70 (d, J = 6.5 Hz, 6H), 2.14 (s, 12H), 3.02 (m,

2H), 3.58 (d, J = 10.1 Hz, 2H), 7.1-7.4 (m, 10H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 9.12 (q), 40.11 (q), 59.07 (d), 63.35 (d), 127.09 (d), 128.17 (d), 129.47 (d), 140.36 (s); HRMS calcd m/z 388.201. Found 388.201.

**(1*R*,2*S*)-2-Dimethylamino-1-phenylpropan-1-ol (*N*-methylephedrine) (3.27)**
Ephedrine (20.0 g, 121 mmol) was dissolved in a mixture of 20 ml formic acid and 20 ml 37% aqueous formaldehyde solution. After refluxing overnight, the mixture was made alkaline by addition of 2N aqueous KOH. The mixture was 3 times extracted with ether and the combined organic layers were washed with brine and dried ($Na_2SO_4$). After evaporation there remained crude **3.27** (21.05 g, 117 mmol, 97%) which was recrystallized from hexane to yield pure **3.27** (19.22 g, 107 mmol, 89%) as glistening needles; mp 87-88° (lit.,[29] mp 87-87.5°).

**Bis-((1*R*,2*S*)-2-dimethylamino-1-phenylpropane-1-)-disulfide (*N*-methylthiolephedrine disulfide) (3.26) from 3.29**
Thiolacetate **3.26** was prepared via the aziridinium ion **3.28** as was described by Dieter.[28] **3.26** (2.92 g, 12.3 mmol) was dissolved in 50 ml of EtOH containing 10 pellets KOH. The mixture was stirred overnight and acidified with 1M aqueous HCl. After 2 extractions with ether the waterlayer was made alkaline again with 2M aqueous KOH and extracted 3 times with ether. The combined organic layers were washed with brine and dried ($Na_2SO_4$). After evaporation crude **3.26** (1.50 g, 3.87 mmol, 63%) was obtained which was recrystallized from EtOH to yield a sample authentical to the one described above.

**Bis-((1*R*,2*S*)-2-(isopropyl-methyl-amino)-1-phenylpropane-1-)-disulfide (3.23)**
Following an analogous procedure as described above *N*-isopropylephedrine (3.10 g, 15 mmol, prepared by alkylation of ephedrine with i-propyl iodide) was converted to the thiolacetate (74%). This thiolacetate was dissolved in 30 ml of MeOH, and HCL was bubbled through for 5 min. After stirring overnight 2N aqueous HCl was added and the mixture was extracted two times with $CH_2Cl_2$. The water layer was made alkaline by addition of 2N aqueous KOH and was extracted three times with EtOAc. The organic layers were washed with brine and dried ($Na_2SO_4$). After evaporation a mixture of **3.22** and **3.23** (2.45 g, 9.24 mmol, 83%) was obtained. This mixture was dissolved in 10 ml of MeOH and air was bubbled through for 1h. After evaporation a part of the so obtained crude **3.23** was purified by column chromatography ($Al_2O_3$ ether/hexane 1:30); $^1H$-NMR and $^{13}C$-NMR identical to to the one described above; Anal Calcd for $C_{26}H_{40}N_2S_2$; C, 70.22; H, 9.07; N, 6.30; S, 14.42. Found: C, 70.17; H, 8.90; N, 6.29; S, 14.43. HRMS; no exact mass could be determined due to fragmentation. Only a small amount of the S-S cleaved product (M = 222) was detected. However, by CI the unfragmented disulfide ($MH^+$ = 445) could be detected.

**(1*R*,2*S*)-2-Dimethylamino-1-phenyl-1-phenylthio-propane (3.30)**
Aziridinium ion **3.28** was prepared from **3.27** (3.0 mmol) as described.[28] After dissolution in benzene, thiophenol (4.0 mmol) was added and the mixture was stirred overnight. Ether was added and after washing 2 times with 1M aqueous KOH and brine the organic layer was dried ($Na_2SO_4$). After evaporation crude **3.30** was obtained which was purified by column chromatography (silica, ether/hexane 1:1) to yield pure material (770 mg, 2.84 mmol, 95%); $^1$H NMR ($CDCl_3$): $\delta$ 1.22 (d, J = 6.6 Hz, 3H), 2.29 (s, 6H), 2.97 (m, 1H), 4.35 (d, J = 6.8 Hz, 1H), 7.1-7.4 (m, 10 H); $^{13}$C-NMR ($CDCl_3$): $\delta$ 11.57 (q), 41.63 (q), 57.64 (d), 64.26 (d), 126.42 (d), 126.68 (d), 128.01 (d), 128.44 (d), 128.52 (d), 131.24 (d), 135.82 (s), 141.80 (s). This sample was identical to a sample prepared by *N*-methylation of **3.13** by B.J. Koning;[30] Anal. Calcd for $C_{17}H_{21}NS$: C, 75.23; H, 7.80; N, 5.16. Found: C, 75.13, H, 7.83, N, 5.10.

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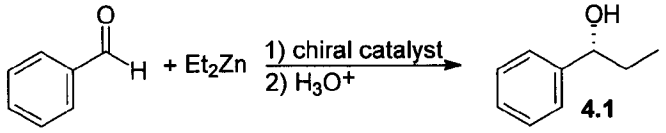
# Chapter 4

# Asymmetric 1,2 additions of diethylzinc to aldehydes catalyzed by β-amino thiols and -disulfides

## 4.1 Introduction

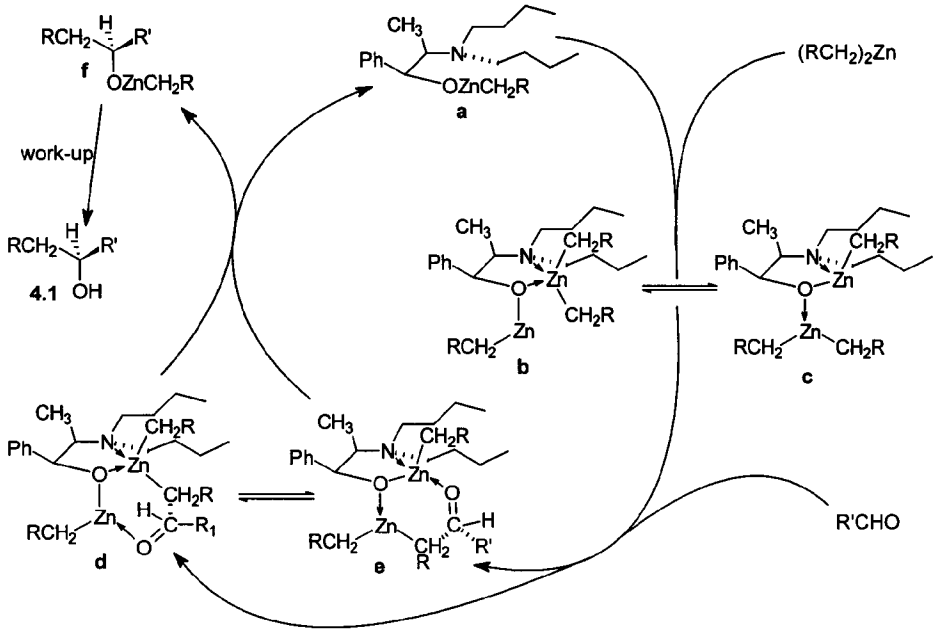
One of the most studied catalytic asymmetric transformations is the 1,2 addition of dialkylzinc reagents to aldehydes like benzaldehyde. Several chiral catalysts have been shown to catalyze this addition, yielding the product **4.1** in excellent enantiomeric excess (>98% e.e.) (scheme 4.1).




*Scheme 4.1 Asymmetric 1,2 addition of diethylzinc to benzaldehyde*

Although the product of the reaction is of little practical interest, it is a nice reaction to study the catalytic properties of newly prepared ligands. However, particularly work of Knochel[1] and Seebach[2] has opened new routes to *functionalized* dialkylzinc compounds. These functionalized zinc reagents have been shown to react with aldehydes also in high enantiomeric excess. The use of such reagents opens a route to more complex chiral alcohols in high enantiomeric purity and thus broadens the scope of this process.
The reaction of scheme 4.1 is easy to perform, reproducible and does not take place in the absence of a catalyst and is therefore an excellent test-reaction. Moreover, the enantiomeric composition of the product is easy to determine by chiral GC, chiral HPLC or optical rotation. Although many types of ligands such as diamines[3] and titanium alkoxides[2] catalyze this reaction, the ligands most often used (with much success) are β-amino alcohols.[4] Another advantage of this 'diethylzinc' reaction is that the mechanism is well known for the use of β-amino alcohols as ligands.
Diethylzinc does not give spontaneous addition to aldehydes due to its rather nonpolar character, originating from its linear *sp*-hybridized geometry.[5] A more polar (and reactive) bent compound may be obtained upon coordination of a electronegative group, or by reaction with a protic residue. Such a bent and activated complex can give addition to an aldehyde. If chiral activating ligands are used, induction may take place upon reaction with an aldehyde. A

mechanism, as was proposed by Soai, for such a reaction is outlined is scheme 4.2 for an ephedrine derivative as chiral ligand.[6]

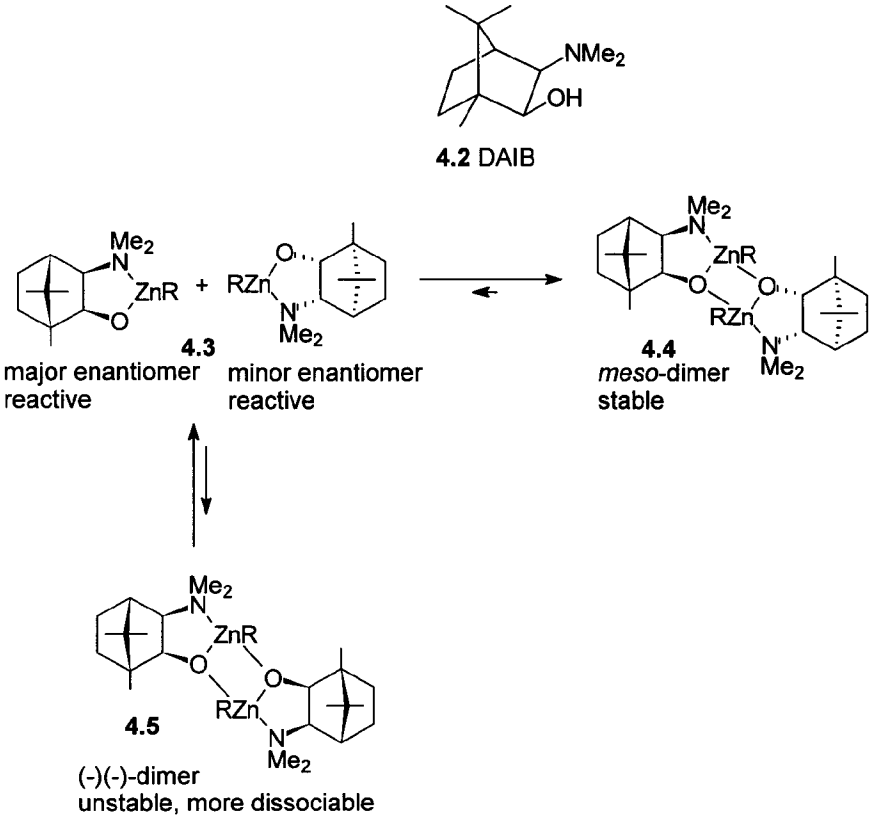



*Scheme 4.2 Proposed mechanism for the diethylzinc reaction*

In a first step the amino alcohol reacts with diethylzinc to yield a monomeric alkylzinc complex **a**. This alkoxide can subsequently form a mono-alkoxide-diethylzinc complex **b** or **c** by reaction with another equivalent diethylzinc. Via an intermediate six-center transition state **d** or **e** the aldehyde is attacked at the *si* face yielding the chiral alkoxide **f**. On work-up this alkoxide is converted into **4.1**.

Special attention has been paid to the so-called non-linear effect. A dramatic example of this effect can be seen upon the use of (-)-3-*exo*-(dimethylamino)isoborneol (DAIB) (**4.2**) as chiral ligand. The use of optically pure catalyst **4.2** leads to the formation of **4.1** with an e.e. of 99%; however, upon the use of **4.2** with an e.e. of only 15% still product **4.1** with an e.e. of 95% could be obtained![7] The reason for this remarkable behavior is outlined in scheme 4.3. The actual catalyst ***4.3*** formed *in situ* is the adduct between **4.2** and diethylzinc. The minor enantiomer of this adduct can form a unreactive dimeric *meso*-complex **4.4** with the major enantiomer. At the same time the major isomer can as well form a dimer with itself to give the optically active dimer **4.5**. The key point is that the *meso*-dimer **4.4** is stable, whereas dimer **4.5** easily dissociates to the reactive monomer **4.3**. In this way the enantiomeric composition of the actual catalyst is dramatically enhanced, increasing the

enantiomeric composition of product **4.1**. The possibility of non-linear effects was first recognized by Horeau[8] and Wynberg.[9]

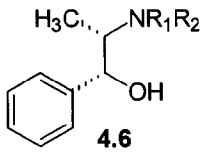



*Scheme 4.3 Rational for the non-linear effect in the diethylzinc reaction*

The use of corresponding mercapto analogs of β-amino alcohols, β-amino thiols, had not been reported prior to our research. This is surprising as thiolates have a high affinity for zinc[10] and might therefore be interesting as chiral ligands for this reaction. In the chapters 2 and 3 we have described several routes to prepare β-amino thiols in optically pure form. Also, we had available some β-amino sulfides and disulfides.[11] Although we intuitively did not expect much from these last classes of molecules in the diethylzinc reaction, we have tested them as ligands as well.

## 4.2 Ephedra alkaloids as ligands in the enantioselective 1,2 addition of diethylzinc to benzaldehyde

The naturally occurring optical pure β-amino alcohol ephedrine (**4.6a**) has been shown by Chaloner[12] to catalyze the addition of diethylzinc to benzaldehyde in reasonable optical purities. Better results were, however, obtained upon the use of *N*-alkyl derivatives of ephedrine **4.6b-e** (figure 4.1).




**4.6**

| compound | $R_1$ | $R_2$ |
|---|---|---|
| **a** | Me | H |
| **b** | Me | Me |
| **c** | Me | Et |
| **d** | Me | n-Pr |
| **e** | Me | i-Pr |
| **f** | n-Bu | n-Bu |

*Figure 4.1 Ephedrine and some of its N-alkyl derivatives*

As can be seen from table 4.1 the best results were obtained using *N*-isopropylephedrine (**4.6e**), which yielded **4.1** in 80% optical purity. Remarkably, the optical purity of **4.1** was dependent on the molar ratio of diethylzinc vs. benzaldehyde. By changing this ratio to 4:1 (instead of 1:1) the optical purity could be increased to 94%.[13]

**Table 4.1. Ephedra catalyzed diethylzinc addition to benzaldehyde**

| compound | **4.6a** | **4.6b** | **4.6c** | **4.6d** | **4.6e** | **4.6e**[a] | **4.6f** |
|---|---|---|---|---|---|---|---|
| yield **4.1** (%) | 60 | 66 | 62 | 63 | 72 | 99 | 100 |
| o.p. **4.1** (%) | 66 | 64 | 77 | 73 | 80 | 94 | 90 |

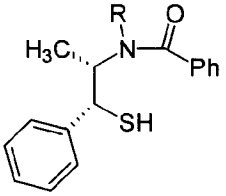
a) a diethylzinc/benzaldehyde ratio of 4:1 was used.

The best ephedra ligand described in literature is, however, *N,N,*-dibutylnorephedrine (DBNE) (**4.6f**), derived from norephedrine, which gives rise to the formation of **4.1** in 90% e.e. without requiring special conditions.[14] Also for several other aldehydes DBNE was shown to be the best ephedra derived catalyst.[6]

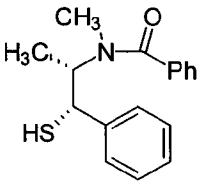
## 4.3 Mercapto derivatives of ephedrine as chiral ligands in the enantioselective addition of diethylzinc to benzaldehyde

From the experiments described in chapter 3 we had some thiolamides **4.7a-c** available, which were prepared by ring opening of aziridines by thiol benzoic acid. Although these compounds were shown to catalyze the desired

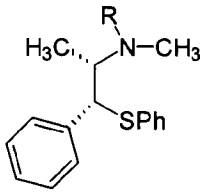
transformation of scheme 4.1, both the conversions and enantioselectivities were rather low (entries 1-3, table 4.2). This is not surprising as these ligands lack the necessary amine functionality to activate diethylzinc. Also sulfide ligands **4.8a-c** (prepared by aziridine ringopening with thiophenol) were shown not to be very reactive.



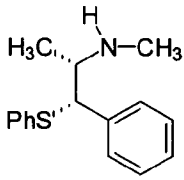

**4.7**
**a** R=$CH_3$
**c** R=H




**4.7b**




**4.8**
**a** R=H
**c** R=trityl




**4.8b**

*Figure 4.2* *β-Thiol amides and β-amino sulfides derived from ephedrine and pseudo-ephedrine*

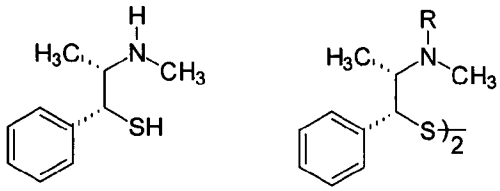
Obviously, a free thiol functionality must be present to form a zincthiolate species (in analogy to alcohols), which is the actual reagent. These sulfides, however, lack this functionality although an amine is present. Although diethylzinc is therefore activated and reaction takes place, no enantioselectivity is observed (entries 4-6, table 4.2).

**Table 4.2. Enantioselective addition of diethylzinc to benzaldehyde**

| entry | ligand | conversion (%) after 40h | configuration of **4.1** | e.e. (%) |
|---|---|---|---|---|
| 1 | **4.7a** | 28 | *R* | 23 |
| 2 | **4.7b** | 59 | *S* | 51 |
| 3 | **4.7c** | 94 | *R* | 3 |
| 4 | **4.8a** | 43 | - | 0 |
| 5 | **4.8b** | 34 | - | 0 |
| 6 | **4.8c** | 14 | - | 0 |

The mediocre results of these ligands in this specific reaction were anticipated. However, recently Bart-Jan Koning, an undergraduate student in our group, has shown[15] that ligands of the type **4.8** are very effective in a palladium catalyzed enantioselective allylation. In this specific reaction enantiomeric excesses of over 80% for the desired product were obtained.

In fact, we expected better results for thiolephedrine (**4.9**) itself as chiral ligand in the reaction of scheme 4.1. Unfortunately, we had, due to its sensitivity to oxidation, only the HCl salt of thiolephedrine at hand. Upon liberation, the free base immediately oxidizes to its disulfide **4.10a**.



**4.9** **4.10**
**a** R=H
**b** R=$CH_3$
**c** R=i-Pr

*Figure 4.3 β-Amino thiols and β-amino disulfides derived from ephedrine*

We had not much faith in the disulfides **4.10** as ligands because they lack the essential free thiol group, which was shown to be necessary from the experiments described in table 4.2. Also the use of a HCl salt is not ideal since chloride can give rise to reduction of the optical yield.[16] Nevertheless the results obtained from both the salt of **4.9** and disulfides **4.10a-c** were most promising (table 4.3).

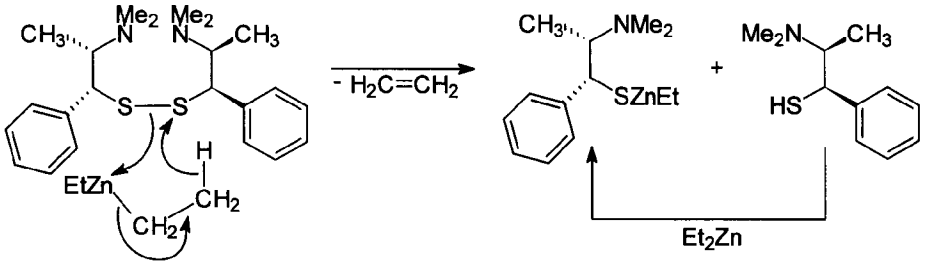
**Table 4.3. Enantioselective addition of diethylzinc to benzaldehyde**

| entry | ligand | conversion (%) after 40h | configuration of **4.1** | e.e. (%) |
|---|---|---|---|---|
| 1 | **4.9**.HCl | 93 | *R* | 80 |
| 2 | **4.10a** | 75 | *R* | 86 |
| 3 | **4.10b** | 97 | *R* | 90 |
| 4 | **4.10c** | 99 | *R* | 89 |
| 5 | **4.10c** | - | - | 94[a] |

a) In this specific case 2-thiophenecarboxaldehyde was used as substrate; after 20 h the conversion was 50%

Especially the results from the disulfides (entries 2-5) are interesting and unanticipated. These ligands are both reactive and enantioselective. This seemed strange at first, but if one considers the reducing properties of diethylzinc (e.g. always a small percentage of benzaldehyde is *reduced* during the reaction to benzylalcohol), one can imagine that a reaction like depicted in

scheme 4.4 takes place.




*Scheme 4.4 Reduction of disulfides by diethylzinc by β-H-elimination*

In our communication presenting the initial results of the diethylzinc reactions described in this chapter[17] this was postulated. We thought that diethylzinc might reduce the disulfide bond yielding the zincthiolate (the catalytically active species), the β-amino thiol (which reacts with another equivalent diethylzinc to the same catalytically active species) and ethene via a β-H-elimination. Recently, Kevin Fitzpatrick, a post-doc in our group, has shown that upon the mixing of benzaldehyde, diethylzinc and disulfide **4.10b** indeed ethene is liberated,[18] giving strong evidence for our postulated disulfide cleavage. However, the ethene liberated amounts only around 10% of the theoretical value. Therefore we now assume that most of the material is cleaved to the zincthiolate and the ethylsulfide. As sulfides are not very active as ligands in the diethyzinc reaction, most of the reaction will proceed *via* the postulated zincthiolate.

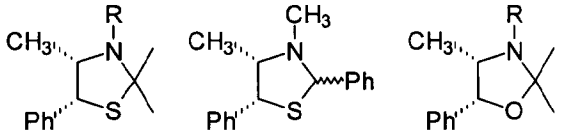
Another notable effect is that the disulfide from thiolephedrine **4.10a** is a better ligand than the corresponding free thiol (as HCl salt), although this probably has something to do with the chlorine being present. Also reactivity does not decrease upon use of disulfides vs. free thiols. As β-amino thiols are usually oxidation sensitive, and therefore difficult to isolate in pure form, it is better to oxidize them completely to the corresponding disulfides, which we have shown to be efficient catalysts. Other (yet unpublished) work from Fitzpatrick has shown that for thiolephedrines a strong non-linear effect can be observed in analogy to DAIB. This gives strong evidence that dimeric (or oligomeric) complexes are formed during the reaction. This is another indication for the cleavage of the disulfides to the corresponding zincthiolates. Surprisingly enough, ephedrine itself showed *no* non-linear effect.

When we compare our results obtained with the (*N*-alkyl)-derivatives of thiolephedrine with those for the natural oxo-ephedrines, it is clear that our ligands are superior. The substitution of oxygen for sulfur increased the e.e. from 66% for ephedrine (**4.6a**) to 86% for the disulfide of thiolephedrine **4.10a**. The effect is even larger for *N*-methylephedrine, for which the e.e. of produced **4.1** goes from 64% to 90%. However, whereas the enantiomeric excess of **4.1**

was shown to be dependent on the benzaldehyde/diethylzinc ratio upon the use of **4.6e** as ligand, our results using the disulfides as ligand was not improved upon changing the stoichiometry of benzaldehyde/diethylzinc and exactly the same e.e. of 89% was obtained. Also decreasing the reaction temperature from room temperature to 0°C had no effect at the enantiomeric composition of **4.1**, which was again obtained in 89% e.e.. It seems that our reactions are not as sensitive to conditions as those of the natural ephedrines. In contrast to their natural analogs, the substitution pattern on nitrogen has hardly an effect on the e.e. of the produced **4.1**, which varies between 86-90% for the thiolephedrines. Also, by analyzing samples at different time intervals we could conclude that the enantiomeric excess always remained constant, independent from the conversion.

### 4.4 Thiazolidines and oxazolidines as ligand for the diethylzinc reaction

Rather to our surprise also our sulfur containing heterocyclic ligands **4.11a,b** and **c** (figure 4.4) were efficient catalysts for the diethylzinc reaction. The tertiary thiazolidine **4.11a** gave **4.1** with an e.e. of 55%, whereas the *N*H-analog **4.11b** gave an e.e. of even 80% (table 4.4).




**4.11**
**a** R=$CH_3$
**b** R=H

**4.11c**

**4.12**
**a** R=$CH_3$
**b** R=H

*Figure 4.4 Thiazolidines and oxazolidines as chiral ligand*

The best result was, however, obtained for thiazolidine **4.11c** (employed as a mixture of diastereomers) which gave **4.1** in 89% e.e.! We are not sure which species might be the actual catalyst prepared *in situ*. Either the observed enantioselectivity might be due to a coordinative effect of diethylzinc to the heterocycle **4.11** or diethylzinc might reduce (partially) the heterocycle (such as **4.11a**) to the *N*-isopropyl analog of thiolephedrine. In the latter case, however, an e.e. equal to **4.10c** would be expected as the same catalytic species would be formed *in situ*. Therefore, after work-up of the reaction we tried to recover the catalyst from the reaction mixture. From the NMR-data it was clear that around 30% of the material was recovered intact, whereas the rest was undefined material. From these NMR-data it was clear that no **4.10c** was present, so reduction of the thiazolidine was ruled out.

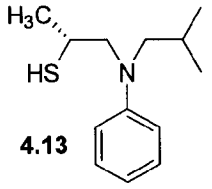
**Table 4.4. The use of thiazolidines and oxazolidines as ligand**

| entry | ligand | conversion (%) after 40 h | configuration of **4.1** | e.e. (%) |
|---|---|---|---|---|
| 1 | **4.11a** | 75 | *R* | 55 |
| 2 | **4.11b** | >99 | *R* | 80 |
| 3 | **4.11c** | 45 | *R* | 89 |
| 4 | **4.12a** | 23 | *S* | 11 |
| 5 | **4.12b** | 48 | *R* | 12 |

To compare our results again with those of the oxygen analogs, we prepared oxazolidines **4.12a** and **b**. From table 4.4 it is clear that their catalytic properties are not significant compared to those observed for **4.11a,b** and **c**. Both reactivity and enantioselectivity are low. Moreover, upon the use of ligands **4.12** the selectivity decreases since around 10% of benzylalcohol is produced during the reaction. Upon recovery of ligands **4.12**, however, no decomposition was observed as concluded by NMR. It is therefore still not clear which species might actually be formed upon the use of ligands **4.11** in this specific reaction.

### 4.5 Other β-amino thiols in the diethylzinc reaction

We have shown that other chiral β-amino thiols derived from thiolactic acid (chapter 2) are efficient catalysts in the reaction of scheme 4.1 as well. For example, compound **4.13** (figure 4.5) gave overnight quantitative formation of **4.1** in an e.e. of 69%.




**4.13**

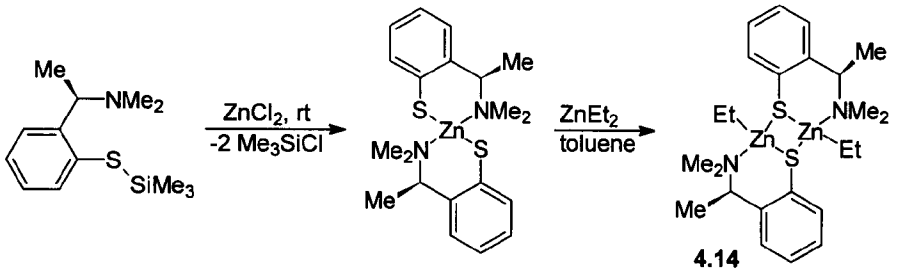
*Figure 4.5 (R)-thiolactic acid derived β-amino thiol*

This is rather remarkable because there is only a small methyl group present on the chiral center. Therefore, we set out to prepare as well other β-amino thiols derived from optically pure α-mercapto acids. Previously, we have shown that these are accessible from the corresponding α-amino acids.[19] Especially, derivatives derived from valine (having an isopropyl substituent at the chiral

center) or leucine (neopentyl group) are interesting. Work on this subject is currently in progress in the group.

### 4.6 Related work by others

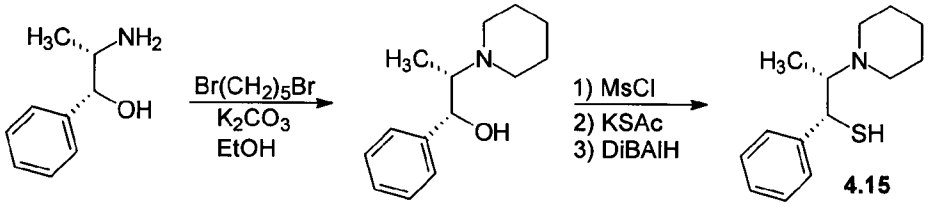
Shortly after we published our paper[17] concerning the enantioselective addition of diethylzinc to benzaldehyde catalyzed by β-amino thiols, two others groups joined the field. Van Koten *et al.* published the use of a zinc complex derived from the chiral thiophenol **4.14** (scheme 4.5) in the diethylzinc reaction.[20]




*Scheme 4.5 Chiral thiophenol ligand as described by van Koten*

Probably, under the reaction conditions, the *bis*(arenethiolate) is converted to a dimeric ethylzinc arenethiolate which is the actual catalytically active species. Using this ligand they achieved an enantiomeric excess for **4.1** of 94%. The best result obtained, however, was for *p*-tolualdehyde, which gave the addition product in 99% e.e..

A ligand system very similar to ours was published by Kang *et al.*.[21] Following the strategy described by Dieter and Dieter[22] (see chapter 3), they converted norephedrine to cyclic amino thiols as **4.15** (scheme 4.6).

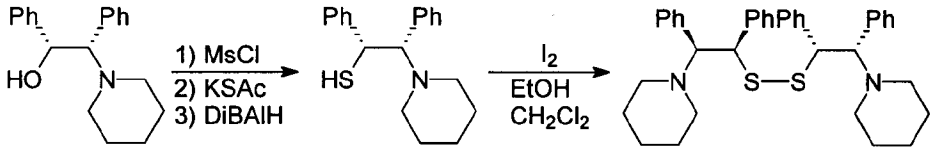



*Scheme 4.6 Ephedrine derived β-amino thiols as described by Kang*

In the publication, Kang, surprisingly enough, states nothing about the oxidation

sensitivity of these compounds. Also the experimental procedure lacks sufficient details to verify the exclusive formation of **4.15** only. However, their ligand system, presumable a mixture of thiol and disulfide, is very efficient and addition of diethylzinc to several aromatic aldehydes gave the products with e.e.'s of >99% in all cases.

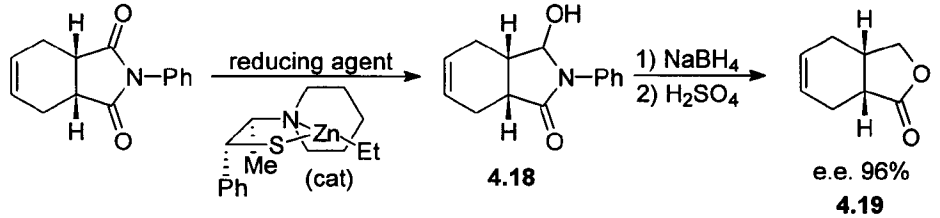
More recently, Kang reported another β-amino thiol (disulfide) system which is very similar to the thiolephedrines.[23] In this article, also Kang states that β-amino thiols **4.16** readily oxidize to the corresponding disulfides **4.17** but, based on our publication,[17] he uses these disulfides as ligands (scheme 4.7). Again the enantiomeric excesses found by him for the addition to several aromatic and α-branched aldehydes are very good (>98% for **4.17** and >99% for **4.16**).




**4.16** **4.17**

*Scheme 4.7 β-Amino thiols **4.16** and -disulfides **4.17** as described by Kang*

Also, Kang used the zincthiolate of thiolephedrine **4.15** as ligand in the catalytic reduction of *meso*-imides.[24] The monoreduced products **4.18** are further reduced to the corresponding hydroxyamides which are converted to the lactones **4.19** by acid catalyzed lactonization. Depending on the substrates and reducing agents, the enantiomeric excesses of the formed lactones varied from 48% to 99% (scheme 4.8). This once again indicates the enourmous potential of β-amino thiols in asymmetric catalysis.




**4.18** **4.19**

*Scheme 4.8 Enantioselective reduction of meso-imides by thiolephedra ligands*

## 4.7 Conclusions

In this chapter we have shown that several β-amino thiols prepared, are efficient catalysts for the 1,2 addition of diethylzinc to benzaldehyde in an enantioselective fashion. Also have we shown that the more stable disulfides can be used as precursors for the preparation of the actual catalyst by reducing the disulfide bond by diethylzinc *in situ*; this goes without loss in chiral discrimination. This important finding was later confirmed by Kang *et al.* for an analogous system.[23] A comparison between our results and the results obtained from 'natural' ephedrines in this specific asymmetric reaction revealed that our ligands are superior in all cases. Also selectivity was independent on several parameters such as the ratio benzaldehyde/diethylzink, temperature, and conversion of the reaction. This indicates that a well defined complex is formed. More surprisingly, we also discovered that thiazolidines are efficient catalysts for the same reaction, again giving the product **4.1** in high enantiomeric excess. A rational for this behavior is not available at this moment. Currently, work is going on in our group to prepare more chiral β-amino thiols and -disulfides as they have shown to be more powerful catalysts than their oxygen analogs. Also, expansion into other catalytic asymmetric carbon-carbon bond forming reactions is now in progress.

**Acknowledgement** The fruitful cooperation with Martin Poelert, Nathalie Peper and Danny Staal is gratefully acknowledged.

## 4.8 Experimental

**General procedure for the 1,2 addition of diethylzinc to benzaldehyde**
Under an atmosphere of nitrogen, diethylzinc (1M in n-hexane, 4 ml, 4 mmol) was added to a solution of 0.1 mmol (5 mol%) of catalyst in dry toluene (10 ml). After stirring for 2 h the mixture was cooled to -20°C and freshly distilled benzaldehyde (0.20 ml, 2 mmol) was added. The mixture was stirred at room temperature and aliquots of 0.3 ml were periodically taken. This sample was filtered over 2 cm silica in a pasteur pipette and washed with 2 ml of $CH_2Cl_2$. Subsequently, the filtrate was analyzed by chiral GC to determine the enantiomeric excess of the produced **4.1**. Enantiomeric excesses were determined using a Hewlett-Packard 5890A gas chromatograph equipped with a 50m WCOT fused silica capillary GC column coated with CP cyclodextrin-B-2,3,6-M-19 (Chrompack No. 7501) and a Hewlett-Packard HP 3396 Series II integrator. Analysis was carried out using an oven temperature of 120°C and an injection- and detection temperature of 200°C. All reactions were performed in duplo and results agreed within experimental error (1%). Enantioselectivity was shown to be dependent neither on catalyst concentration nor progress of the reaction.

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# Chapter 5

# Enzymatic catalysis in organic solvents

## 5.1 Introduction

A whole range of reactions performed daily by chemists all over the world have been performed in nature from times dating long before the appearance of man. Also organic chemists have discovered the major benefits of *catalysis*. Nature, being economical as it is, has been working with its own catalytic toolbox for already thousands of years. One of the major components of this toolbox consists of a wide scala of proteins -- enzymes -- capable of performing a multitude of transformations under mild conditions. Among these reactions are the most fundamental organic transformations such as *hydrolysis, oxidation, reduction* and *C,C bond* formation. It is therefore not surprising that organic chemists try, more and more, to make of use of this bio-toolbox for their own needs. Their efforts during the last several decades, and even more importantly, the efforts from colleagues in neighboring disciplines such as biochemistry, molecular biology and genetic engineering have provided so much information that the use of enzymes in organic chemistry is no longer a technique being limited to the expert. The availability of excellent theoretical and practical textbooks on enzymology for organic chemists makes routine use of enzymes now possible for everyone.[1,2,3]

As was stated in the introductory chapter, asymmetric catalysis is an elegant method to make enantiomerically enriched products using only a small amount of chiral catalyst. These catalysts can either be synthetically prepared but more and more chemists are starting to use natural enzymes as well. Enzymes are capable of enormous rate enhancements of up to $10^{10}$. This aspect and the fact that enzymes (being built up from optically pure amino acids) are enantiomerically pure makes them very interesting as chiral catalysts in organic transformations.

Enzymes can be classified according to the transformations they catalyze *in vivo*. For example, enzymes can catalyze oxidative and reductive processes (oxireductases) or C,C bond formation (aldolases, synthetases). Enzymes that catalyze these reactions are often cofactor dependent, therefore reactions are not so easily performed in an *in vitro* environment. Another class of enzymes are hydrolytic enzymes such as amidases, esterases and lipases. During the last decade much work has been devoted to possible applications of this class of hydrolytic enzymes in organic transformations. Special attention has been paid to esterases and lipases, which are now available in bulk quantities for reasonable prices. Since they are not cofactor dependent and tolerate a wide

range of substrates (still remaining enantioselective) they are ideal catalysts for organic transformations. Therefore, we will focus on the use of lipases and esterases in organic chemistry.

## 5.2 Natural action of lipases

Lipases are hydrolases which in nature catalyze the hydrolysis of lipids to fatty acids and glycerol. This hydrolysis takes place at the water-lipid interface. Below the critical micellar concentration of a specific lipid no reaction occurs. Therefore, it was suggested that lipases might undergo a conformational change at the interface. Indeed it was shown that in water the active site was capped with a lid which opened upon binding of a specific inhibitor.[4] The open form is believed to be equivalent to the form at the oil-water interface. In this open form the substrate is transferred into the active site where hydrolysis takes place via a *reversible* mechanism. Due to the large excess of water present, the equilibrium is shifted to the hydrolysis side. As lipases have a broad substrate specificity, many unnatural substrates can be hydrolyzed by lipases as well. One of the major bulk applications of lipases is therefore the use in washing detergents as stain (grease) removers. If one considers the use of lipases for ester hydrolysis on a laboratory scale, one has to take in mind that for each ester molecule being hydrolyzed a molecule of carboxylic acid is produced. This means that the pH of the solution will decrease during reaction. As the activity of lipases is very sensitive to changes in the pH, one has to compensate for the acid being released. Therefore, reactions usually are performed in a buffer of the optimum pH for the lipases, and by continuous addition of base by automatic titration to maintain a constant pH. Such reaction conditions are environmently friendly but special (expensive) equipment is needed.

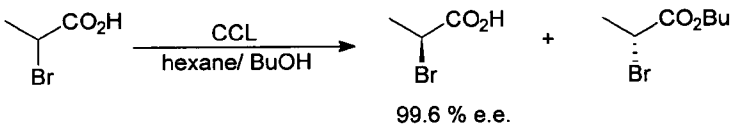
## 5.3 Lipases in organic solvents

Hydrolysis of esters by lipases is a reversible process. To form an ester from a carboxylic acid and an alcohol, the problem is to shift the balance for such a reaction from hydrolysis to esterification. Clearly, water must be removed from the reaction mixture to shift the equilibrium. A way to do so is the use of organic solvents for lipase catalyzed transformations. Pioneering work by Klibanov has indeed shown that it is possible in this way to use lipases for the reverse process.[5] The use of an organic solvent has several advantages above the use of water, namely:

- organic substrates are (usually) soluble, whereas the enzyme is insoluble. Therefore, the product and enzyme are easily recovered by non-extractive methods, thereby improving the yield.
- water sensitive substrates can be used.

- the equilibrium of the reaction is shifted; esters and amides can be prepared.
- enzymes are thermally more stable since water that could hydrolyze the enzyme peptide bonds is not present. Conformational unfolding is reduced.
- the enzyme becomes more rigid, and thus sometimes more selective.
- there is no pH-effect; simple laboratory equipment can be used.

Although lipases need an essential amount of water to maintain their catalytic active conformation, only several dozen molecules of water (varying from lipase to lipase) are needed to do so. The bulk-water of the reaction media can therefore be omitted. Although it may seem bizarre at first sight, the best organic solvents to carry out enzymatic transformations are the most hydrophobic ones as they do not strip the essential bounded water from the enzyme. More hydrophilic organic solvents may remove the essential water from the lipases and, consequently, destroy its active conformation. Also, enzymes are not soluble in organic solvents and their conformational flexibility is frozen. They retain the conformation from the aqueous solution they were isolated from (at a certain pH). Klibanov has also shown that by employing an organic solvent for enzymatic esterfications excellent enantioselectivities can be achieved. For example, he showed that 2-halocarboxylic acids (see chapter 2 for applications of this synthon in thiolactic acid chemistry) can be esterified in the presence of Candida cylindracae lipase (CCL) with very high enantioselectivity (scheme 5.1).[6]



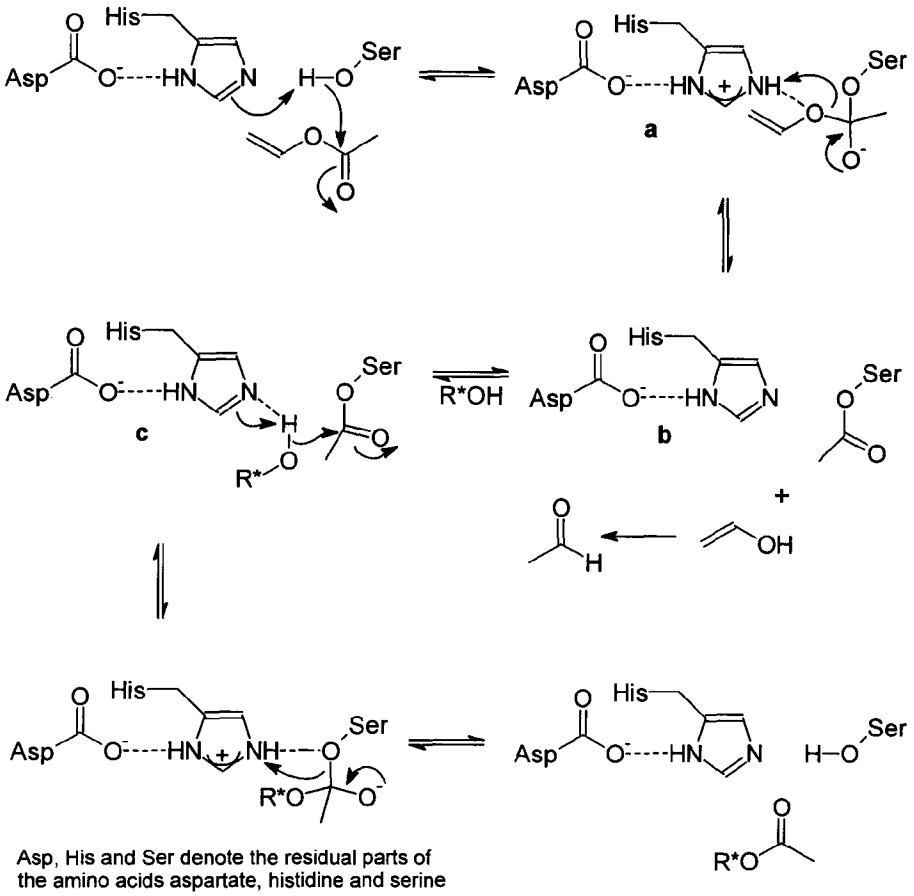

*Scheme 5.1 Enzymatic resolution of 2-halocarboxylic acids*

Especially the pioneering work from Klibanov has opened the eyes of many organic chemists all over the world and has caused a major boom in the use of enzymes in organic solvents to prepare many interesting molecules in optically pure form.

### 5.4 Enzyme kinetics and enantioselectivity

From the Eyring equation[7] it follows that for a reaction to proceed, the reactant molecules first must overcome a Gibbs energy barrier. The Gibbs energy needed to overcome this barrier in the rate limiting step is called the energy of activation, $\Delta G^{\ddagger}$. The reaction rate of an enzymatically catalyzed reaction is

enhanced by reducing $\Delta G^{\ddagger}$ by the lipase. This means that the lipase stabilizes the transition state of a specific reaction. To do so, the enzyme has to bind the substrates in a specific region where it can catalyze the desired transformation. This location of the enzyme is called the active site. Hydrolytic enzymes, such




*Scheme 5.2 Mechanism of lipase catalyzed acylation using vinyl acetate*

as lipases, have devised a catalytic triad which enables them to speed up hydrolytic reactions enormously. In this class of enzymes there are four catalytic types known; serine proteases, thiol proteases, metallo proteases and aspartyl proteases. Since most lipases are serine proteases the mechanism of such a catalytic pathway will be dealt with in more detail.

Because most of the reactions we have carried out are irreversible acylations of

alcohols using vinyl acetate,[8] the mechanism of such an acylation of an alcohol will be described instead of the hydrolysis of a natural ester (scheme 5.2).
The active site of serine proteases contains a catalytic triad of the amino acids Asp, His and Ser, in which the Ser acts as the incoming nucleophile. The other two amino acids are spatially positioned to transfer very rapidly a proton from the Ser to Asp, to make the Ser more nucleophilic. In this charge-relay system the basic nitrogen of histidine abstracts a proton from the serine (making it more nucleophilic) and in its turn transfers its acidic proton to the remote aspartate. In this way the histidine acts as a proton-relay. Also there is a so called oxyanion hole present, in which the amino acid backbone of the enzyme can stabilize the tetrahedral intermediate **a**. The exact positioning of substrates, the stabilization of the transition state and the rapid proton transfer from Ser to Asp via His, makes these enzymes very efficient catalysts. After formation of the tetrahedral intermediate **a** between the enzyme and vinyl acetate, vinyl alcohol is released and an enzyme-acyl intermediate **b** is produced. All these reaction steps are in principle reversible. However, vinyl alcohol immediately gives rise to irreversible formation of acetaldehyde via rapid keto-enol tautomerisation. In this way the equilibrium is shifted from the substrate to the enzyme-acyl intermediate **b**. An incoming nucleophile, such as an alcohol, can now react with the enzyme-acyl intermediate to form another tetrahedral intermediate **c**. The desired acetate of the alcohol is subsequently liberated, and the enzyme is regenerated to its original form, capable of undergoing another cycle. As this whole process takes place in the chiral active site of a lipase, there are diastereomeric interactions upon reaction of a racemic alcohol. In a recent study Kazlauskas has shown, by covalently binding two transition state analogs for the hydrolysis of both enantiomers of a menthol ester in the active site of Candida rugosa lipase, that the slower reacting enantiomers in fact disrupts the catalytic triad by forcing the imidazole ring of the His to rotate 60°.[9] This disruption of the catalytic triad for one of the enantiomers is the cause for the chiral discrimination in this enzymatic resolution. Probably this is a general mechanism for chiral recognition by lipases, as the results are fully in agreement with the empirical rule formulated by Kazlauskas previously.[10] This rule states that all lipases have the same enantiopreference for a specific substrate, but the enantioselectivity is different varying from lipases to lipase. Depending on the size and shape of both enantiomers, there will be a difference in reaction speed due to deactivation of the catalytic machinery by one of the enantiomers. A high enantioselectivity means a large difference in reaction rate between the two enantiomers. If the difference in reaction rate is significantly large, at a certain time all of one enantiomer will have been consumed by the lipase, and the remaining substrate will be enantiomerically pure. This means, in contradiction to asymmetric catalysis, that for such a kinetic resolution, always enantiomerically pure material can be obtained if there is a difference in reaction rate for the enantiomers. The only problem is that with decreasing difference in reaction rate, the conversion of the reaction will have to increase to obtain

enantiomerically pure starting material. In the ideal case, however, the difference in Gibbs energy for the diastereomeric transition states becomes so large, that only one enantiomer will react. In that case, at 50% conversion (for a racemate) both the remaining substrate and the produced ester are enantiomerically pure. From Michaelis-Menten kinetics one can derive a series of equations which relate the factors such as the enantiomeric excess of the substrate and the product, the conversion and the enantiomeric ratio (E). This enantiomeric ratio E, which is a constant, is in fact the ratio between specifity constants of each enantiomer and is defined by equation 1,

$$E = \frac{V_A/K_A}{V_B/K_B} \tag{1}$$

in which $V_A$, $K_A$ and $V_B$, $K_B$ denote the maximum velocities and Michaelis constants of the fast and slow reacting enantiomer. This E-factor can be correlated to the conversion (c) and the e.e. of the starting material (ee(S)) and the e.e. of the product (ee(P)) according to equation (2).[11]

$$E = \frac{\ln[(1-c)(1-ee(S))]}{\ln[(1-c)(1+ee(S))]} = \frac{\ln[1-c(1+ee(P))]}{\ln[1-c(1-ee(P))]} \tag{2}$$

Although it may be easy to determine the conversion by experimental techniques such as NMR or GC, it can also be calculated from equation 3, once the e.e.'s of starting material and product have been determined experimentally.

$$c = \frac{ee(S)}{ee(S)+ee(P)} \tag{3}$$

The formulas of equation 2, correlating the conversion and the theoretical enantiomeric excesses of starting material and product, can be plotted for several E-values and are highly indicative for the efficiency of enantioselective resolutions (figure 5.1).[12]

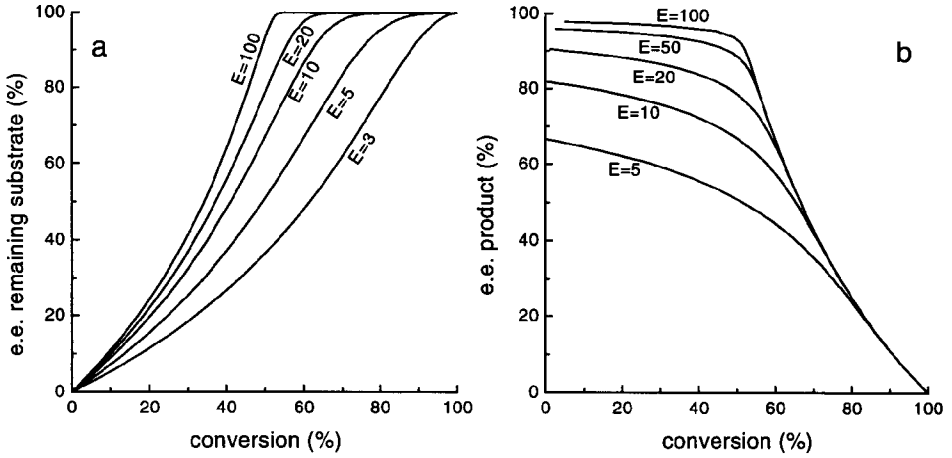
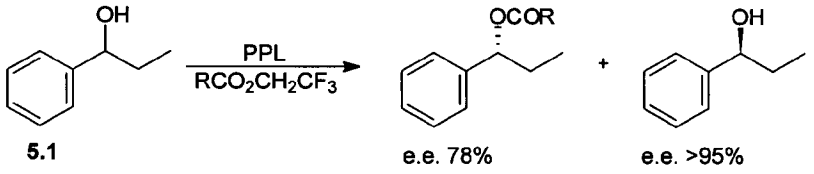



*Figure 5.1a and b* *Enantiomeric excess of starting material and product vs. the conversion at different E-values*

From figure 5.1a it can be seen that independent from the E-value enantiomerically pure starting material can be always obtained, although yields decrease significantly when the E-value becomes small (<10). From a preparative point of view the E-value should be between 10-20 to make a resolution interesting (chemical yield ± 40%), but more interesting are E-values of above 50, for which the chiral discrimination becomes very large. If E>100 then the recognition is almost absolute, and both starting material and product are nearly optically pure at 50% conversion. In this way the maximum yield of optically pure material can be obtained. On industrial scale, often the undesired enantiomer is racemized and recycled into the process to increase yields. As can be seen from figure 5.1b it is hard to obtain optically pure product, unless E is really large; for E values <50 even at low conversion the e.e. of the formed product is already <95%.

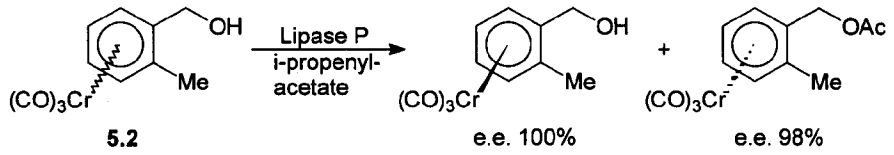
### 5.5 Several examples of lipase catalyzed resolutions in organic solvents

In organic solvents lipases are capable of resolving acids, ester, amides, peroxides, amines and thiols, however, alcohols are most often resolved. For example, the cheap PPL can catalyze the acylation of secondary alcohols **5.1** in ether with enantiomeric ratio's E of over 100 (scheme 5.3).[13] In this way, many interesting chiral alcohols (e.g. used as building blocks in total synthesis) have been resolved by lipases in the last couple of years.



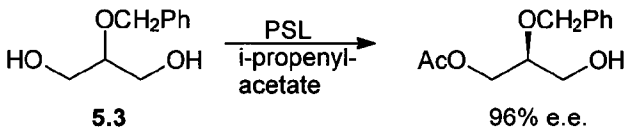

*Scheme 5.3 Lipase catalyzed resolution of secondary alcohols*

The methodology is not restricted to simple organic molecules; organometallic compounds such as tricarbonyl($\eta^6$-arene)chromiums **5.2** have been resolved as well, for example, by lipase P (scheme 5.4).[14]



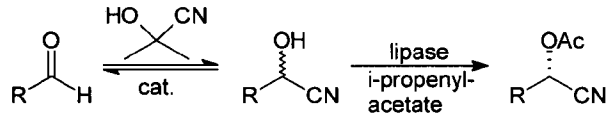

*Scheme 5.4 Lipase P catalyzed resolution of organometallic compounds*

Resolution is not only limited to racemates; *meso* and prochiral molecules such as 2-*O*-benzyl-glycerol **5.3** have been resolved by the so-called 'meso trick'. The lipase reacts preferentially with one of the enantiotopic alcoholic groups of the achiral **5.3** and an optically enriched monoacetate is produced (scheme 5.5). In theory, a 100% chemical yield *and* enantiomeric excess can be achieved.




*Scheme 5.5 Lipase catalyzed asymmetrization of prochiral 2-O-benzyl-glycerol*

Another way to improve the chemical yield of the reaction is *in situ* racemization of the starting material. This has been shown to be useful for racemization prone cyanohydrins, which were acylated in the presence of a lipase (scheme 5.6). In this way an enantiomeric excess of 91% of the acetate was obtained at 81% conversion.[15]

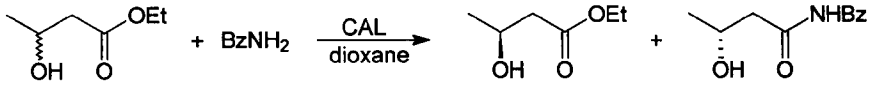



*Scheme 5.6 Enzymatic acylation of racemization prone cyanohydrins*

The best result for such an enzymatic racemization-resolution process was, however,

recently achieved in our laboratories. It was shown that certain substrates were resolved by lipases with enantiomeric excesses >98% at conversions above 80%. As this process may be patented in the near future more details can't be revealed at this moment.[16]

Resolution by lipases in organic solvents is not only limited to alcohols, but acids, amines and amides can be resolved as well. For example, esters of type **5.4** can be transaminated in the presence of Candida antarctica lipase (CAL) with E>100 (scheme 5.7). The amides so produced have subsequently been converted to interesting 1,3-amino alcohols by reduction.[17]




**5.4** 82% e.e. >99% e.e.

*Scheme 5.7 Lipase catalyzed enantioselective amidation*

Esters can even be transformed to primary amides by gaseous $NH_3$ in organic solvents by certain lipases.[18] The use of lipases has also been extended to other unnatural substrates such as peroxides,[19] hydrazines[20] and other compounds, indicating that the use of lipases in organic chemistry is highly versatile. Although this short overview is but a small selection of possible applications of lipases in chiral resolutions, it indicates nevertheless the enormous possibilities which can be achieved with the use of these biocatalysts in organic solvents. In the following two chapters the results we obtained with the use of lipases in organic solvents will be described.

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12. Figure 5.1a can be computer generated by rearranging equation 2 to $c = 1 - \{(1 - ee(S)) / ((1 + ee(S))^E)\}^{1/(E - 1)}$. Figure 5.1b can be computer generated by relating the variables c and ee(P) to a function of x for values of $0 \leq x \leq 1$ and $c = 1 - x/2 - x^E/2$ and $ee(P) = (x - x^E)/(2 - x - x^E)$.

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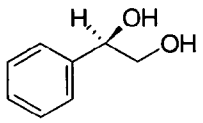
# Chapter 6

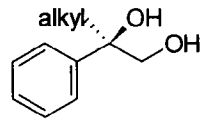
# Lipase catalyzed resolution of α,α-disubstituted glycols

## 6.1 Introduction

Optically pure glycols such as (*R*)-1-phenylethane-1,2-diol (**6.1**) are important building blocks in asymmetric synthesis. They are easily converted to epoxides,[1] aziridines[2] and amino alcohols,[3] all compounds which have shown their value in asymmetric synthesis in recent years. Applications of this type of vicinal diols as ligands are known as well,[4] and they have been used for the enantiomeric excess determination of chiral ketones by acetal formation.[5] Straightforward methodologies have been developed to prepare these vicinal diols in enantiopure form,[6] but the compounds which we are interested in, namely glycols having a tertiary (rather than the usual secondary) chiral center, cannot be prepared following these strategies. Optically pure tertiary diols of the general structure **6.2** are barely known in the literature (figure 6.1).[a]




(*R*)-**6.1**




**6.2**

*Figure 6.1 Optically pure secondary and tertiary glycols*

From a German patent of Bayer, however, it is clear that the compounds **6.2** serve as building blocks for the synthesis of triazole derivatives, which show strong fungicide and growth regulating activities.[7] These activities depend on the absolute configuration of the chiral center. It is therefore important to find pathways to this type of diols in enantiomerically pure form. The most trustworthy route to prepare such optically pure tertiary diols is that described in the patent. This approach relies on the Seebach procedure (see chapter 2) starting from optically pure mandelic acid as is described in more detail in section 6.10.[8] Other routes to optically pure diols of type **6.2** have been reported, which rely as well on the use of expensive

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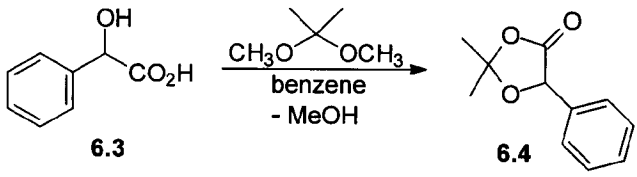
[a] In this chapter mainly the alkyl chain on the 2-position in compounds **6.2** is functionalized. For clarity in nomenclature, we have chosen to use phenylethane-1,2-diol (**6.1**) as parent compound ('phenylglycol') and use substitutive nomenclature with the 2-position designated as α. Correct IUPAC nomenclature is used in the experimental section.

(optically pure) reagents, and laborious multi-step procedures.[9]
An efficient method to prepare vicinal diols in (usually very high) enantiomerically enriched form is the *cis*-dihydroxylation of alkenes as described by Sharpless.[10] Although this methodology has also been applied to several *gem*-di-substituted alkenes, only one diol of type **6.2** (derived from α-methyl styrene) has been prepared in good enantiomeric excess.[11] Therefore, we looked for a more general approach to resolve racemic tertiary 1,2-diols **6.2** into the optical antipodes. Since we had already gained some experience in our group with the use of esterases and lipases for the enantioselective hydrolysis of α-alkylated mandelic- and lactic acids[12] and the regioselective deacylation of mercapto acids (chapter 2),[13] we wondered whether we could expand this protocol to the resolution of α-alkylated glycols as well. The best known technique nowadays to resolve alcohols in antipodes consists of enantioselective acylation of these alcohols by biocatalysts in *organic solvents.* The major advantages of changing the solvent from water to organic solvents have been outlined in the previous chapter. However, before one can resolve a racemic mixture, one has to prepare it. This is described in the next section.

## 6.2 Synthesis of racemic α-alkylphenylglycols.

Not only are routes to optically pure tertiary diols **6.2** scarce in literature, but also synthesis of the racemates have barely been described. Although some of the compounds we prepared were already known, they all have been synthesized by different processes. Some of them were reported as a by-product of a reaction. One approach worth mentioning is the electrochemical hydroxymethylation of aldehydes and ketones with paraformaldehyde. This methodology, however, makes use of a large *excess* of the rather expensive $VCl_3$.[14] Although the method is elegant and very clean, it is uneconomical to perform on larger scale. The method we developed appears to be general, and gives the desired compounds in high yield using simple chemical transformations. The method consists of converting an α-hydroxy acid, such as racemic mandelic acid (**6.3**), to the 1,3-dioxolane-5-one **6.4**.



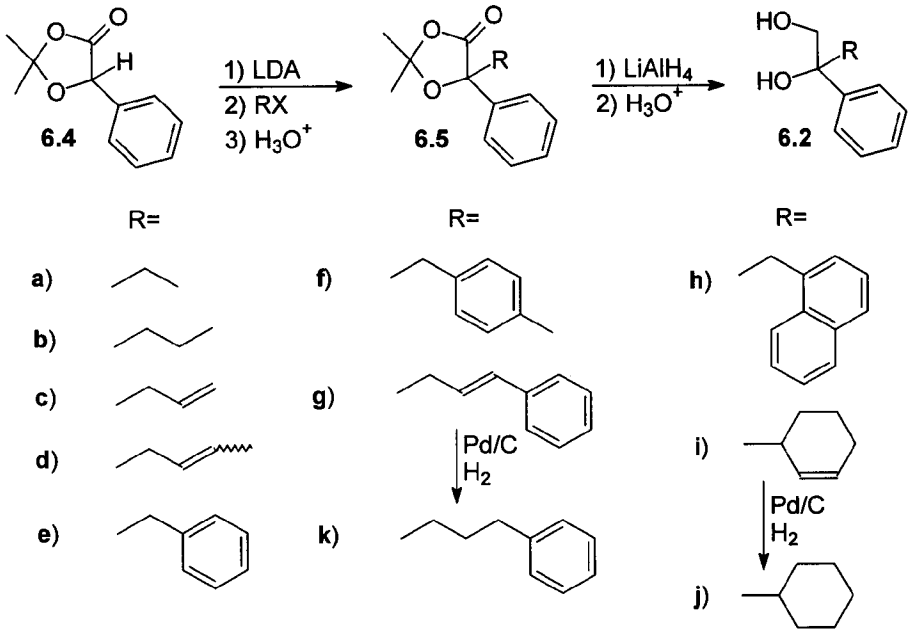

**6.3** **6.4**

*Scheme 6.1 Synthesis of dioxolanone **6.4** from mandelic acid*

Although this transformation has been performed by a condensation with acetone in the presence of mineral or Lewis acids, a better way is to make use of

dimethoxypropane under azeotropic conditions. Under these neutral conditions methanol is slowly distilled off, and by monitoring the temperature of the distillate the progress of the reaction can be determined. No work up other than removal of excess solvent is needed to isolate the product (scheme 6.1).

As already shown by Moorlag,[12] **6.4** is easily deprotonated by LDA under anhydrous conditions, and the generated enolate can be trapped smoothly by various alkyl halides to give a range of α-alkyl-1,3-dioxolane-5-ones **6.5** in good yields (scheme 6.2).




*Scheme 6.2 Synthesis of diols **6.2** by alkylation of **6.4** followed by reduction*

The method is, however, limited to primary alkyl halides and allylic- or benzylic halides. Secondary and tertiary alkyl halides, as well as branched primary alkyl halides fail to give the reaction due to steric repulsion. Some of the reagents which were not capable of giving the reaction of scheme 6.2 are i-propyl iodide, t-butyl iodide, i-amyl bromide, phenylethyl bromide, cyclohexyl bromide and bromomethyl dioxolane. Reaction with chloromethylnaphthalene to give **6.5h** proceeded only partially (even at room temperature overnight) so the yield was not satisfactory. The α-cyclohexyl derivative **6.5j** which is not accessible via direct alkylation has been prepared via the use of the allylic alkyl halide α-bromo-cyclohexene. The produced **6.5i** was subsequently reduced to **6.5j** by catalytic hydrogenation.

Several of the α-alkylated dioxolanones **6.5** had been prepared before by Moorlag

as precursor for α-alkylated mandelic acids.[12] These can be prepared from **6.5** by hydrolysis of the acetal functionality. However, under reductive conditions using $LiAlH_4$ the dioxolanones **6.5** can be reduced to the corresponding α-alkylated diols **6.2** (scheme 6.2). This reaction proceeded very well and gave our desired diols in ,generally, good overall yields starting from cheap racemic mandelic acid (table 6.1).

**Table 6.1. Synthesis of diols 6.2 from dioxolanone 6.4**

| entry | alkyl halide employed | product | reducing agent | yield (%) |
|---|---|---|---|---|
| *1* | ethyl iodide | **6.2a** | $LiAlH_4$ | 83 |
| *2* | n-propyl iodide | **6.2b** | $LiAlH_4$ | 52 |
| *3* | allyl bromide | **6.2c** | $LiAlH_4$ | 73 |
| *4* | crotyl bromide | **6.2d** | $LiAlH_4$ | 60 |
| *5* | benzyl bromide | **6.2e** | $LiAlH_4$ | 92 |
| *6* | α-bromoxylene | **6.2f** | $LiAlH_4$ | 81 |
| *7* | cinnamyl bromide | **6.2g** | $NaBH_4$ | 67 |
| *8* | 1-chloromethylnaphthalene | **6.2h** | $LiAlH_4$ | 21 |
| *9* | 3-bromo-cyclohexene | **6.2i** | $LiAlH_4$ | 64 |

This methodology using $LiAlH_4$ was shown to be effective for all the α-alkylated dioxolanones **6.5** except for the cinnamyl derivative **6.5g** in which the conjugated double bond was partially reduced to alkane **6.2k** as well. A solution to this problem was found in the use of $NaBH_4$ in a mixture of t-BuOH/ MeOH,[15] which selectively reduced only the dioxolanone-ring and not the conjugated alkene, to cleanly give **6.2g**. The conjugated double bond of this cinnamyl derivative can subsequently be reduced using Pd/C and $H_2$ to give **6.2k**.

### 6.3 Lipase catalyzed resolutions; experimental setup

In the literature, extensive precedents can be found for the enantioselective acylation of alcohols. In the previous chapter a representative series of reactions and factors governing reactivity and enantioselectivity was discussed. In this section we will give an introduction about how we have set up our experiments. Whereas the success of most asymmetric transformations is judged from the e.e. of the produced material, this is of less importance in kinetic resolution experiments where the e.e. is dependent on the conversion of the reaction. Very important in this respect is the enantiomeric ratio (E), which is the ratio of reaction rates of both enantiomers of the starting material.[16] When the difference in reaction rate is high,

the value of E becomes larger indicating a better enantiodifferentiation. This E-value, which is in theory a constant during the reaction, can be calculated from the e.e.'s of the starting material and the product. Also the conversion of the reaction can be determined from both e.e.'s (see section 5.4). It is therefore important to find an easy and accurate way to determine the enantiomeric excess of *both* components. For most of our diols **6.2** and the corresponding enzymatically produced acetates **6.6** the e.e. could be determined by chiral HPLC.[17] Determination of the enantiomeric excesses using this technique was always first performed on the racemate to optimize base-line separation. In this way also exact retention times of both enantiomers are known and no errors are made upon interpreting results obtained from enantiomerically enriched samples. By appropriate modification of the eluent and the flow rate in most cases even the crude reaction mixture could be analyzed directly and all four peaks resulting from both enantiomers of the diol and both enantiomers of the produced acetate could be detected separately in a single run.[18] A further advantage of this accurate and fast technique is that because of its sensitivity only very small quantities of material are needed for analysis. This opens the way to perform the enzymatic resolutions on analytical scale, making screening of various enzymes easy. For screening purposes we had a library of sixteen lipases available. The lipases most often used in literature were all present in this library. The exact composition of the library is given in table 6.2. Most of these lipases were a generous gift from Amano Europe Ltd, which is gratefully acknowledged.

Enantioselectivity of lipase catalyzed acylation is not only dependent on the substrate and lipase employed, the solvent and acylating reagent used are important for chiral discrimination as well. When one envisions the possible combinations of testing twenty diols, sixteen lipases, ten solvents and five different acylating reagents, over fifteen thousand (!) experiments would have to be performed. Also more subtle effects arising from temperature, concentration, the way of stirring and administration of the biocatalyst (e.g. in its immobilized form) can influence the enantiomeric ratio. Therefore one has to seek for the optimum in each parameter, to reduce the total amount of experiments which have to be performed to arrive at the best results.

From the literature it is known that for lipase catalyzed acylations one of the best irreversible acylating reagents is vinyl acetate.[19] We, therefore, started our experiments using this specific acyl donor. As an organic solvent we chose the more often employed diisopropyl ether (dipe). Under these 'standard' conditions the resolution of diols **6.2** (scheme 6.2) was examined using the lipases from table 6.2. Reactions were run on a 0.3 mmol scale (about 50 mg of diol) in 1 ml of dipe containing 0.3 ml of vinyl acetate. About 25 mg of lipase was used as biocatalyst. This seems to be quite a lot (50% w/w), however, considering the high molecular weight of these peptides and the 'dead' ballast in these crude and/or immobilized biocatalysts the actual molar percentage is less then 1‰![20] This is truly a catalytic approach. Conversions were initially determined by TLC (silica, ether/hexane 1:2).

At sufficient conversion a sample was taken, which was analyzed by chiral HPLC to determine exact conversions and enantiomeric ratios.

**Table 6.2. Lipases and their origin**

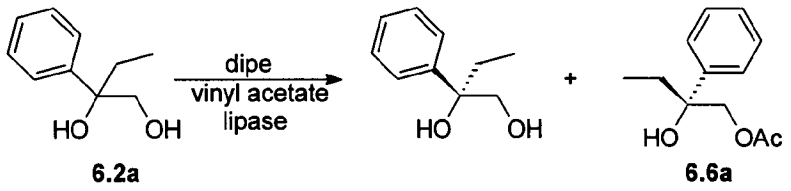
| Lipase | Source | Supplier |
|---|---|---|
| A | *Aspergillus niger* | Amano |
| AKG | *Pseudomonas sp.* | Amano |
| AY | *Candida rugosa (cylindracae)* | Amano |
| CE | *Humicola lanuginesa* | Amano |
| D | *Rhizopus delemar* | Amano |
| G | *Penicillium camembertii* | Amano |
| GC | *Geotrichum candidum* | Amano |
| L | *Candida lipolytica* | Amano |
| M | *Mucor javanicus* | Amano |
| N | *Rhizopus niveus* | Amano |
| PS | *Pseudomonas fluorescens (cepacia)* | Amano |
| R | *Penicillium roqueforti* | Amano |
| CCL | *Candida cylindracae* | Sigma |
| PPL | *Pig pancreas* | Sigma |
| HPL | *Hog pancreas* | Sigma |
| CAL | *Candida antarctica* | Novo |

### 6.4 Lipase catalyzed resolutions of α-ethyl- and α-propylphenylglycol

The first compound we tried to resolve was α-ethyl diol **6.2a**. Since we had no idea which lipase would be best suited for this reaction, we tested all sixteen (scheme 6.3).

From these results it was clear that nearly all lipases were capable of performing the desired transformation. What we, however, observed from the NMR data was that (even on prolonged reaction times of several weeks) only the primary alcohol was acylated. Due to steric repulsion, acylation of the tertiary hydroxyl group never was observed. This siteselectivity was general for all tertiary diols **6.2** examined.

As can be seen from table 6.3, unfortunately, none of the 16 lipases tested showed good enantiodiscrimination. The best result was obtained for lipase GC (E = 9), whereas the others showed E-values lower than 4. The reaction times




**6.2a** **6.6a**

*Scheme 6.3 Lipase catalyzed resolution of α-ethyl diol **6.2a** in dipe*

needed to reach satisfactory conversions were rather disappointing, all varying from 1 day to up to 1 month(!), whereas secondary alcohols **6.1** require several hours to days. Probably this has to do with additional steric repulsion upon introduction of an alkyl side chain at the chiral center.

**Table 6.3. Lipase catalyzed resolution of 6.2a in dipe using vinyl acetate**

| lipase | reaction time | conversion (%) | e.e. alcohol (%) | e.e. acetate (%) | E |
|---|---|---|---|---|---|
| A | 1 month | 50 | 19 | 19 | 1.7 |
| CCL | 17 h | 100 | - | - | - |
| D | 1 month | 57 | 27 | 20 | 2.7 |
| G | 1 month | 12 | <5 | <5 | <1 |
| R | 1 month | 39 | 13 | 20 | 1.7 |
| HPL | 17 h | 28 | <5 | <5 | <1 |
| CE | 15 h | 15 | 10 | 56 | 4.0 |
| CAL | 17 h | 97% | - | - | - |
| AKG | 17 h | 13 | <2 | 7 | 1.2 |
| GC | 17 h | 46 | 58 | 67 | 9.3 |
| L | 1 month | <5 | - | - | - |
| PS | 1 month | 18 | <2 | <2 | <1 |
| PPL | 1 month | 23 | 3 | 10 | 1.3 |
| N | 1 month | <5 | - | - | - |
| M | 1 month | 54% | <5 | <5 | <1 |
| AY | 17 h | 94% | - | - | - |

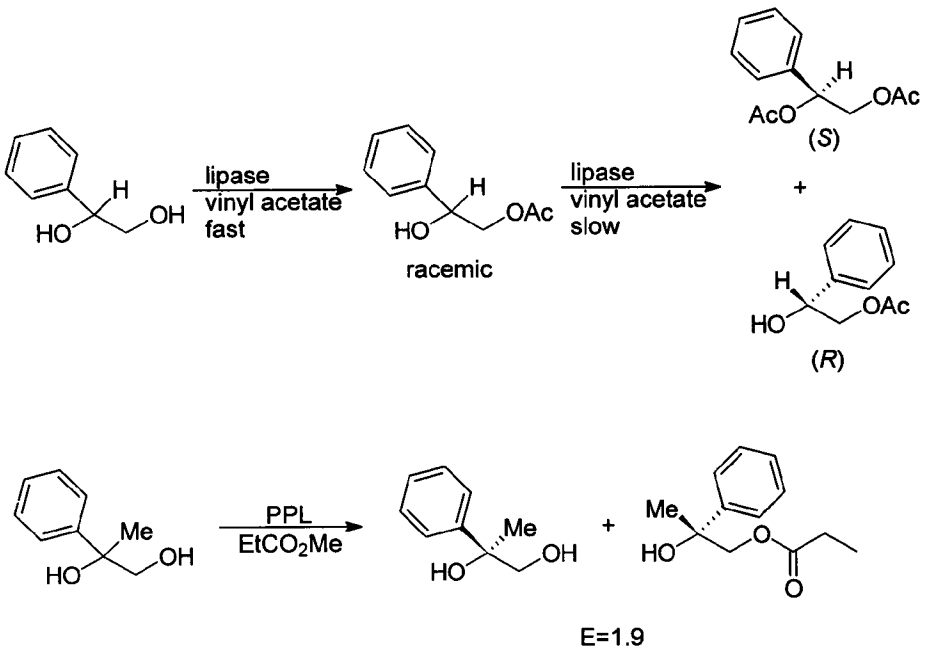
Lipases CAL, CCL and AY were very reactive for diol **6.2a**, and gave quantitative racemic product overnight. This is interesting when one considers the siteselective preparation of the monoacetate **6.6a** in *racemic* form. Also at lower conversions, these lipases were not enantioselective.
The same trend was observed for $\alpha$-propyl diol **6.2b**. Although the reactivity of the lipases seemed somewhat higher, again chiral discrimination was low. Lipase GC, which showed moderate discrimination for the previous substrate, lost this preference for diol **6.2b**. Note that lipase AKG is hardly selective for **6.2a** and **6.2b**. This lipase will become more important later on.
Representative results from the lipase catalyzed resolutions of diol **6.2b** are summarized in table 6.4.

**Table 6.4. Lipase catalyzed resolution of 6.2b in dipe using vinyl acetate**

| lipase | reaction time | conversion (%) | e.e. alcohol (%) | e.e. acetate (%) | E |
|---|---|---|---|---|---|
| GC | 24 h | 58 | 41 | 30 | 2.7 |
| A | 24 h | 20 | 6 | 24 | 1.7 |
| G | 24 h | 7 | 4 | 50 | 3.4 |
| AKG | 24 h | 8 | <2 | <2 | <1 |
| R | 24 h | 18 | 11 | 51 | 3.3 |
| M | 24 h | 9 | <2 | <2 | <1 |
| CE | 44 h | 43 | 12 | 16 | 1.5 |
| HPL | 44 h | 26 | 11 | 8 | 2.1 |

When we take a closer look at the literature it is not surprising to find such low enantioselectivities. For example, Theil has shown in several papers that for secondary glycols both hydroxyl groups are acylated.[21] In the first step the primary hydroxyl group is acylated in a rapid process, in which hardly chiral discrimination takes place. In a subsequent step the secondary alcohol (at the chiral center) reacts. Chiral recognition was shown to take place during this step (scheme 6.4). This makes sense since chiral discrimination is expected to be larger upon reaction near the chiral center. Our chiral center in compounds **6.2** is tertiary and due to steric repulsion no reaction takes place there; therefore, we are not in a position to expect high enantiodiscrimination. Our process can be considered as only the first (non-enantioselective) step of the Theil reaction. Similar phenomena have been observed by Zwanenburg *et al.*, who also found dramatically low chiral recognition upon acylating $\alpha$-methylphenylglycol.[22] The enantiomeric ratio of E = 1.9 they observed is in good correlation with our results (scheme 6.4).

Clearly, the strategy for resolution we were following was a bad one. Fortunately, we encountered more success in using other substrates.

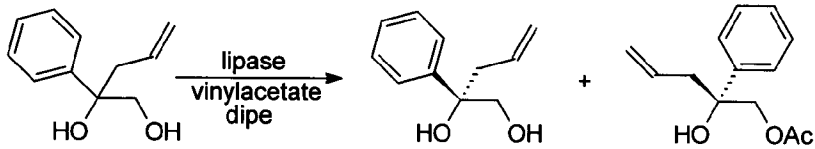



*Scheme 6.4 Resolution of phenylglycol and α-methylphenylglycol*

### 6.5 Lipase catalyzed resolutions of α-allylphenylglycol

The third substrate we tested was α-allyl diol **6.2c** (scheme 6.5). This diol has about the same size as **6.2b** but a major difference is that it has an unsaturated chain. As chiral discrimination by lipases is mostly considered as being dependant on size and shape of molecules, we expected about the same behavior of diol **6.2c** as was observed for **6.2b**.

Indeed, as can be seen from table 6.5, most of the lipases showed the same (low) enantioselectivity for **6.2c** as for **6.2a** and **b**. However, the positive exception was lipase AKG. This specific lipase showed no enantiodiscrimination for **6.2a** and **b** ($E \simeq 1$) but a rather good selectivity of $E = 15$ for **6.2c**. Also, the enantioselectivity did not drop upon longer reaction times. At 60% conversion the remaining diol had already an enantiomeric excess of 94%!




**6.2c** (*S*)-**6.2c** (*R*)-**6.6c**

*Scheme 6.5 Lipase catalyzed resolution of α-allyl diol* ***6.2c***

**Table 6.5. Lipase catalyzed resolution of 6.2c in dipe using vinyl acetate**

| lipase | reaction time | conversion (%) | e.e. alcohol (%) | e.e. acetate (%) | E |
|---|---|---|---|---|---|
| A | 44 h | 31 | 21 | 46 | 3.4 |
| AY | 24 h | 100 | - | - | - |
| CE | 24 h | 19 | 8 | 34 | 2.2 |
| CAL | 24 h | 91 | <2 | <2 | <1 |
| GC | 44 h | 54 | 61 | 53 | 5.7 |
| HPL | 24 h | 38 | 19 | 31 | 2.3 |
| AKG | 44 h | 27 | 31 | 82 | 15 |
| AKG | 5 d | 60 | 94 | 62 | 15 |
| PS | 24 h | 30 | 29 | 69 | 6.9 |
| PPL | 24 h | 22 | 15 | 52 | 3.8 |

After this success, we tried to perform the same reaction on preparative scale. Scaling up of this type of reactions is known to be difficult sometimes. The problem lies in the stability of the biocatalyst, and reactivity usually decreases on prolonged reaction times owing to mechanical denaturation of the biocatalyst; also inhibition by substrate, product and/or solvent cannot be completely ruled out. This is indeed what we observed for the preparative resolution of diol **6.2c**. Diol **6.2c** (3.4 mmol) was acylated by 150 mg of lipase AKG but the conversion after 10 days was only around 25% as judged from TLC. Reactivity had clearly significantly been reduced upon scaling-up of the reaction from 0.3 to 3.4 mmol. The remaining diol was nevertheless isolated by column chromatography and by comparison of the optical rotation with literature values we could conclude that the isolated diol had an optical purity of 17% and that the (*R*)-enantiomer had been consumed preferentially. The remaining diol was (*S*) and the acetate formed therefore (*R*). To

obtain optically pure material in this way one has to find a way to stabilize the lipase under the reaction conditions. One of the techniques to stabilize lipases in organic solvents consists of immobilization of the enzyme on a carrier material. Indeed, we found it was possible to immobilize lipase AKG on celite and in this way to enhance its stability. The results of these immobilization experiments are described in detail in section 6.12.

### 6.6 Lipase catalyzed resolution of α-crotylphenylglycol

After the resolution experiments with **6.2c**, we had some idea about which lipases might be both reactive and enantioselective for the transformations desired. Especially lipase AKG seemed very interesting and we decided to do more experiments with this lipase. First we wanted to know whether the unsaturated part of **6.2c** was important for the chiral recognition by lipase AKG, and, therefore, we prepared α-crotyl derivative **6.2d**. The crotyl bromide which we used for the α-alkylation was a mixture of *Z*- and *E*-alkene in about a 1:2 ratio. Therefore, **6.2d** was a mixture of *Z*-and *E* isomers also. On chiral HPLC these isomers could not be seen separately, but with chiral GC both enantiomers of the *E*-and *Z*-alkene could be detected separately. The enantiomers of the enzymatically produced esters, however, proved to be inseparable under these conditions. Again lipases such as AY and CAL were shown to give fast reaction without enantioselectivity. Within one day all starting material was converted to the (racemic) monoacetate.

**Table 6.6. Lipase catalyzed resolution of 6.2d in dipe using vinyl acetate**

| lipase | *E/Z* | conversion (%) | e.e. alcohol (%) | e.e. acetate (%)[a] | E |
|---|---|---|---|---|---|
| A | *E* | 58 | 57 | 41 | 4.1 |
| A | *Z* | n.d. | n.d. | n.d. | n.d |
| CE | *E* | 54 | 13 | 11 | 1.4 |
| CE | *Z* | 35 | 18 | 33 | 2.4 |
| GC | *E* | 64 | 80 | 45 | 6.1 |
| GC | *Z* | 77 | 90 | 27 | 4.6 |
| AKG | *E* | 59 | 94 | 65 | 16 |
| AKG | *Z* | 59 | 57 | 40 | 4 |

[a] The e.e. of the acetate could not directly be determined but was calculated instead from e.e.(acetate) = {e.e.(alcohol)/conversion-e.e.(alcohol)}. The conversion was determined by GC.

Some other lipases did catalyze the reaction more slowly, but again enantioselectivity was rather low (table 6.6). The only positive exception again was lipase AKG in case of reaction with *E*-**6.2d**. Again a good enantioselectivity of

E = 16 was observed. From these results there appears to be something unique about lipase AKG. Out of 16 lipases it is the only one which is capable of giving satisfactory chiral discrimination upon acylation of the primary alcohol situated relatively far from the chiral center. This recognition seems, however, to be based on the presence of an unsaturated residue, which probably interacts in the active site. This is a unique observation compared to literature data for enzymatic resolutions. Nearly always, the steric demand of a group is considered to be the main factor governing stereoselectivity. This can be seen for some active site models of several lipases in which the size of the different substituents on the chiral center is taken into account as the major factor governing stereoselectivity.[23] Another factor which is known to give dramatic effects in enzymatic acylations is the solvent employed. We initially chose dipe, but now wondered whether the chiral recognition could be enhanced by changing the solvent. Therefore we examined the resolution of **6.3c** in several organic solvents ranging from polar to apolar (section 6.7).

### 6.7 The effect of the organic solvent and acylating reagent on lipase AKG catalyzed resolution of α-allyl diol 6.2c

For lipase catalyzed resolutions it has been shown that there can be huge differences on changing one solvent for another. For example, reactivity can change due to the water stripping effect of a solvent.[24] Also, enantioselectivity can be highly dependent on the solvent used. Sometimes good correlations between enantioselectivity and, for example, the dielectric constant of the solvent can be found.[25] It was argued that in less polar solvents the rigidity of the enzyme is greater and that therefore it can adapt only to one of the enantiomers. Under polar conditions this rigidity is more loose and therefore the enzyme becomes more flexible. Due to this flexibility the steric constraints upon interaction with the substrate are more relaxed and therefore the enantioselectivity decreases. Although this may be a nice explanation, the argumentation does not seem to be generally applicable because there are systems known in which no correlation at all between solvent parameters and enantioselectivity can be found.
Therefore, we tested a range of ten solvents ranging from polar to apolar ones for the resolution of **6.2c** with lipase AKG. In general we can say that going from polar to more apolar solvents the reactivity *and* enantioselectivity of this particular reaction increase. For example, in the polar solvent acetonitrile after 94 h only 16 % conversion was achieved with an E of 5. After the same reaction time in benzene the conversion was already 42 % and the corresponding E was 24 (!) (table 6.7). Also in n-hexane and n-pentane reasonable enantiomeric ratios were observed. The good enantioselectivity in benzene remained constant during the reaction and at 52% conversion the remaining alcohol had already an enantiomeric excess of 85%, which corresponds to an enantiomeric ratio of 22. From these experiments we conclude that benzene is the best solvent to carry out our

resolution experiments, although our initial choice, the less carcinogenic dipe, is a good alternative.

**Table 6.7. Lipase AKG catalyzed resolution of 6.2c in different solvents using vinyl acetate**

| solvent | $\epsilon_r^{26}$ | reaction time (h) | conversion (%) | e.e. alcohol (%) | e.e. acetate (%) | E |
|---|---|---|---|---|---|---|
| acetonitrile | 35.9 | 94 | 16 | 12 | 65 | 5 |
| THF | 7.58 | 94 | 18 | 16 | 71 | 7 |
| EtOAc | 6.02 | 94 | 19 | 17 | 71 | 7 |
| ether | 4.20 | 69 | 31 | 35 | 79 | 11 |
| chloroform | 4.81 | 164 | 30 | 33 | 77 | 11 |
| $CH_2Cl_2$ | 8.93 | 164 | 24 | 26 | 84 | 13 |
| pentane | 1.84 | 69 | 35 | 44 | 82 | 15 |
| hexane | 1.88 | 69 | 29 | 34 | 83 | 15 |
| mtbe | 4.50 | 138 | 35 | 44 | 80 | 15 |
| toluene | 2.38 | 138 | 36 | 47 | 85 | 18 |
| dipe | - | 188 | 53 | 84 | 74 | 18 |
| benzene | 2.27 | 94 | 42 | 62 | 87 | 24 |
| benzene | 2.27 | 164 | 52 | 85 | 77 | 22 |

Although a nice trend can be observed going from polar to the more apolar solvents a linear relationship between several solvent parameters, such as the dielectric constant ($\epsilon_r$, see table 6.7), dipole moment and logP, and the enantiomeric ratio could not be found.

Also the acylating reagent is known to have an effect on reactivity and enantioselectivity. Most often irreversible acylating reagents such as the enol-esters vinyl acetate or isopropenyl acetate are used for resolutions of alcohols, but reactive anhydrides, glycerol esters or activated esters can be used also. Therefore, we tested 5 different acyl donors for the resolution of diol **6.2c** employing lipase AKG in dipe. From table 6.8 it can be seen that our initial choice, vinyl acetate, was indeed the best. Although isopropenyl acetate showed a better chiral discrimination of $E = 23$ compared to vinyl acetate ( $E = 14$), the reactivity was much lower. For this reason it is not attractive to use this specific acyl donor for resolution purposes. Ethyl acetate was shown to be unreactive and the activated esters trichloroethyl acetate and acetic anhydride were reactive but not enantioselective. This lack of stereospecificity is the result of a competing non

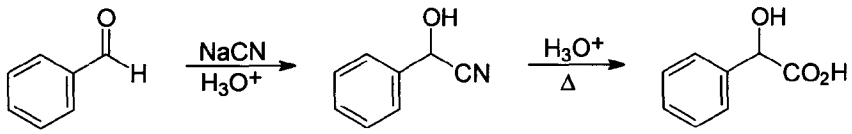
catalyzed reaction. In the absence of lipase AKG these last two acylating reagents were shown to give spontaneous formation of the acetate at room temperature. In contrast, vinyl acetate gave even after 10 days not a trace of the product in the absence of a biocatalyst.

**Table 6.8. Lipase AKG catalyzed resolution of 6.2c in dipe using several acyl donors**

| acyl donor | time (d) | conversion (%) | E |
|---|---|---|---|
| vinyl acetate | 5 | 30 | 14 |
| isopropenyl acetate | 13 | 9 | 23 |
| ethyl acetate | 20 | <2 | - |
| trichloroethyl acetate | 8 | 18 | 2 |
| acetic anhydride | 6 | >98 | - |

### 6.8 Para-substituted α-allylphenylglycols

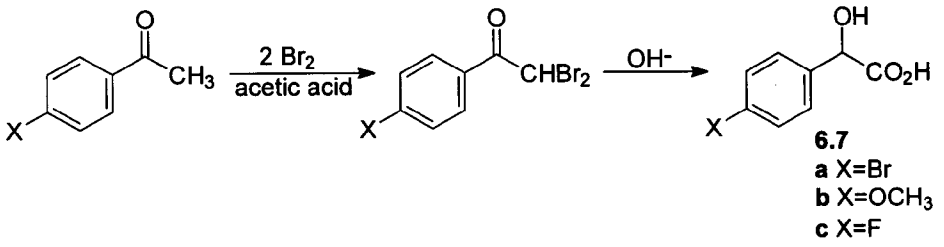
After the optimization of solvent and acyl donor for the resolution of diols **6.2** using lipase AKG we considered whether the chiral discrimination could be improved by substituents on the aromate ring. Increasing the bulk on an aromatic ring is sometimes known to give better enantioselectivities.[21a, 23a] Using the synthetic procedure outlined in section 6.2, it is easy to make derivatives having different α-alkyl chains. Substitution of the aromatic ring means that one has to start with another mandelic acid analog. One of the oldest and most straightforward methods of preparing α-hydroxy acids, such as mandelic acid, is via the hydrolysis of a cyanohydrin. These cyanohydrins can easily be prepared from an aldehyde and sodium cyanide under acidic conditions (scheme 6.6).[27]




*Scheme 6.6 Synthesis of mandelic acid via the cyanohydrin*

A major drawback of this reaction, however, is the use of the poisonous sodium cyanide and the price of some of the substituted benzaldehydes. An elegant alternative, is the double α-bromination[28] (or chlorination[29]) of a substituted

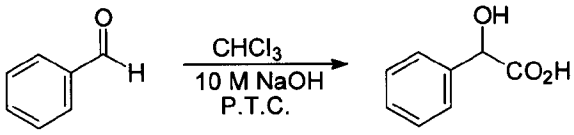
acetophenone with bromine in acetic acid. These bis-bromides (or chlorides) are crystalline materials and are easy to purify. Under alkaline conditions the *gem*-bromide is *in situ* converted into the aldehyde, which subsequently rearranges via an intramolecular *Cannizzaro*-type reaction to the α-hydroxy acid (scheme 6.7).[28]




**6.7**
**a** X=Br
**b** X=$OCH_3$
**c** X=F

*Scheme 6.7 Synthesis of mandelic acids via double bromination and hydrolysis*

Using this approach *p*-bromo (**6.7a**), *p*-methoxy (**6.7b**) and *p*-fluoro mandelic acid (**6.3c**) were synthesized in about 50% yield. Also another, more recent, approach was used to prepare the substituted mandelic acid analogs. This method consists of generating under alkaline phase transfer conditions (P.T.C.) dichloro carbene, which adds to an aldehyde. The dichloro epoxide formed is immediately hydrolyzed under the very alkaline conditions to the α-hydroxy acid (scheme 6.8).[30]



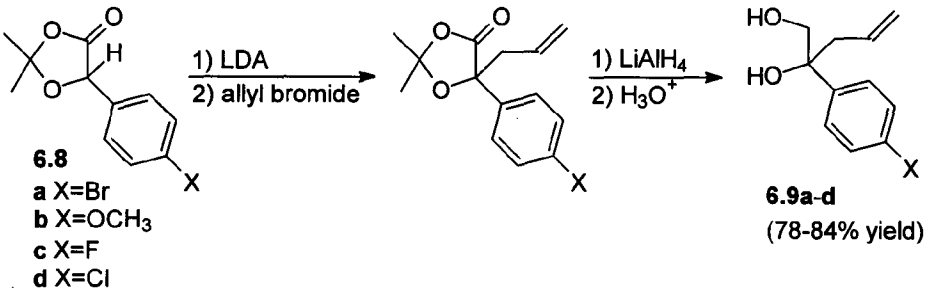

*Scheme 6.8 Synthesis of mandelic acids via dichloro carbene addition to aldehydes*

Although being a nice one step procedure, which avoids the use of cyanide, it turned out that yields were only moderate and that in our hands the previous described method was superior.

Following the procedure described in scheme 6.7 we also tried to prepare *p*-nitro mandelic acid, but those attempts unfortunately failed. *p*-Chloro-mandelic acid was obtained from Janssen Chimica.

By means of the procedure outlined in scheme 6.2 the substituted mandelic acids were converted to their corresponding dioxolanones **6.8a-d**, which were subsequently α-allylated and reduced to give the substituted α-allylphenylglycols **6.9a-d** in overall good yields (scheme 6.9).

Under identical conditions as for diol **6.2c**, diols **6.9** were acylated by lipase AKG.




**6.8**
**a** X=Br
**b** X=$OCH_3$
**c** X=F
**d** X=Cl

**6.9a-d**
(78-84% yield)

*Scheme 6.9 Synthesis of substituted diols **6.9***

The substitution of a proton at the *para* position by a larger group had a dramatic influence. The built up chiral recognition for **6.2c** was nearly completely lost for **6.9a**, **b** and **d** (table 6.9). The cause for this unexpected effect may be both steric and electronic. Either introduction of a substituent on the *p*-position makes the substrate too large to give a nice fit within the active site of the lipase, therefore decreasing chiral recognition, or the introduction of an electron donating substituent on the aromate decreases favorable interactions with the active site. Therefore we prepared substrate **6.9c**, which bears a *p*-fluorine residue. Fluorine has about the size of a proton, but has more or less the 'electronic' character of bromine and chlorine. From the results from derivative **6.9c** it is clear that the lost discrimination can be partially recovered upon introduction of the *p*-fluoro group. This means that there is a significant steric effect. However, electronic contributions cannot completely be ruled out as well, because the enantiomeric ratio is only 8 compared to 15 for **6.2c**.

**Table 6.9. Lipase AKG catalyzed resolution of substituted diols 6.9 in dipe using vinyl acetate**

| compound | reaction time (h) | conversion (%) | e.e. alcohol (%) | e.e. acetate (%) | E |
|---|---|---|---|---|---|
| **6.2c** | 44 | 27 | 31 | 82 | 15 |
| **6.9a** | 48 | 14 | 5 | 31 | 2 |
| **6.9b** | 24 | 11 | 4 | 34 | 2 |
| **6.9c** | 96 | 22 | 21 | 74 | 8 |
| **6.9d** | 72 | 8 | 5 | 56 | 4 |

Besides dipe as solvent also some others (including benzene) were tested but no

remarkable effects on the (low) chiral discriminations were observed.

### 6.9 Lipase AKG; a crude model

From the data gathered so far, it is clear that chiral recognition for most lipases is only marginal. Lipase AKG is the only lipase capable of giving good discrimination and that only for very specific substrates (**6.2c**, *E*-**6.2d** and **6.9c**). The reason for the specificity of this lipase is not known, but the unsaturated part in the side chain is without doubt important. Also substitution in the aromatic ring is not well tolerated by lipase AKG. Therefore, we concluded that this lipase must have something specific compared to the other lipases in its active site giving stabilizing interactions with the unsaturated part. However, since a 3D-structure of the active site of this specific lipase is not available, we only could come up with some kind of empirical model which could account for our results.
A popular way to envision interactions between the active site of an enzyme and a substrate consists of drawing an active site model consisting of 'pockets', which give an indication of the size and the shape of the molecules tolerated in the active site. The dimensions of these pockets are determined by the results of series of molecules tested. In this way a nice model has been proposed by Jones for Pig Liver Esterase (PLE).[31] This model is known to have a high predictive value in enzymatic hydrolysis experiments using this esterase. Also for the resolutions of α-alkylated mandelates using PLE, Moorlag has shown that the observed stereoselectivity indeed can be accounted for using this model.[12] In recent years, Jones has explored the boundaries of his model to make its dimensions more accurate. His latest update of the model is now considered by him to be the final one in which the exact dimensions of the pockets are known.[32] To make such an accurate model one has to have a large series of results available, stemming from different types of molecules. This is possible for PLE because it is one of the most frequently applied biocatalysts in organic chemistry. The successful application of lipase AKG for resolution of racemates has, however, seldom been reported in literature. There are, however, some reports on lipase AK (also from Amano), but at this moment we are not sure whether this lipase is identical to lipase AKG.[33] However, for lipase AK there has been proposed a crude model[34] which postulates that the active site is 'flat' because of its preference for the resolution of near planar (unsaturated) molecules. It is indeed surprising that most molecules that are resolved with good chiral recognition ($E > 20$) by lipase AK have some kind of unsaturation somewhere in their backbone. Also for the molecules that we find to be resolved reasonably by lipase AKG the α-alkyl side chain has some kind of unsaturation in it, giving it conformational rigidity and a certain degree of flatness. One of the pockets is therefore assumed by us to be a flat one, in which only nearly planar side chains, in an extended conformation, can be positioned. This pocket is designated as the F (flat) pocket. The site where reaction takes place, at the primary hydroxyl group, is pictured as the R (reaction) pocket. The other pocket

in which the phenyl group is positioned is the S (small) pocket. From experiments with diols **6.9** and lipase AKG we know that an increase of the bulk on the para position of the aromatic ring makes the group too large to give a good interaction with the lipase. The size of the F pocket is not known. We do know, however, that the *E*-diol **6.2d** is resolved with good recognition (E = 16), whereas the *Z*-diol is resolved with an enantiomeric ratio of only 4.
This might have to do with the fact that such an *Z*-alkene geometry pierces through the boundaries of the F pocket. In figure 6.2 our model for lipase AKG, based on the results of the diols described above, is depicted and both enantiomers of diol **6.2c** are placed in this model. In can be seen that the (*R*)-enantiomer gives a nice fit of the allyl group, being stabilized in the (F)lat pocket, and of the phenyl group in the (S)mall pocket. Positioning of the (*S*) enantiomer in the same model, however, leads to a loose fit of the allyl group in the S pocket and the necessity of placing the phenyl group in the F pocket is improper since it has not the correct size. The fit for this enantiomer not ideal and therefore the (*R*)-enantiomer will be acylated by preference.

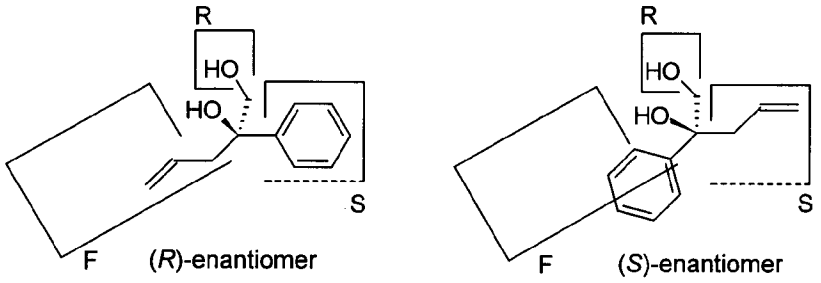



*Figure 6.2 Active site model for lipase AKG*

From the same model it can be concluded that non-planar side chains such as ethyl and n-propyl do not give a good fit in the F pocket for the (*R*) enantiomers since they are not flat, whereas for the (*S*) enantiomer the phenyl group does give a good fit in this pocket. Therefore, **6.2a** and **6.2b** are not acylated selectively. Introduction of a sterically demanding group on the para position of the aromatic ring (as for **6.9a,b** and **d**) destabilizes interaction of the phenyl group in the S pocket (the substrate is too large), and neither enantiomers will be acylated preferentially resulting in a low chiral recognition. For *Z*-**6.4** the methyl group might reach through the boundaries of the F pocket (which is not the case for the *E* form) therefore decreasing chiral recognition (figure 6.3).
There might even be a physical basis for this model. Helpfull discussions with Dr. D. Lang and Prof. B.W. Dijkstra[35] at our university, have provided us with insight in the actual shape and size of the active site of *Pseudomonas* lipases. They have determined the structure of both the open and the closed form of a lipase from

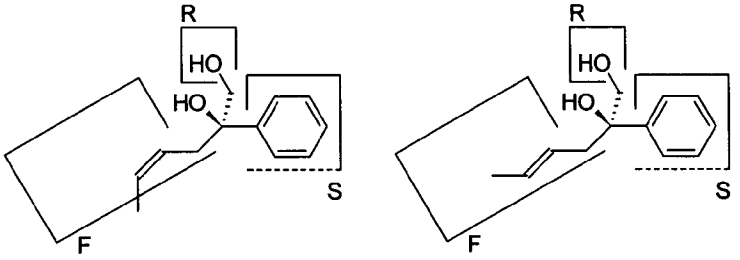



*Figure 6.3 Application of the lipase AKG model for the (R)-enantiomer of E- and Z-**6.4***

*Pseudomonas Glumae* in their group.[36] Although the chance that this specific lipase is identical to lipase AKG is small, there might be enough homology to justify comparison of our model with this 3D-structure. It is clear that in the active site of *P. Glumae*, there is, relatively close to the catalytic machinery and the oxyanion hole, a rather polar position which can accommodate the tertiary hydroxyl group. Moreover, there are two hydrophobic regions which can accommodate our alkyl substituents. One (smaller) hydrophobic region is positioned to the back and could bind the phenyl group; a larger hydrophobic region is positioned to the front. This region might accommodate larger alkyl fragments, in our case the allyl group. In this specific lipase this hydrophobic region is wide enough to accommodate all kinds of hydrophobic groups. Our lipase AKG might, however, have an additional insertion in the peptide sequence and therefore this specific region might be deformed in such a way that only flat molecules can be embedded. Although this is pure speculation, it might be an explanation of the unique character of lipase AKG. Moreover, the spatial positions of the hydrophobic regions in the lipase from *Pseudomonas Glumae* are similar to the ones described in our model and as a consequence it predicts the same stereochemical outcome of our transformations as compared to the model.

## 6.10 Making use of the lipase AKG model

After taking a closer look at the model, we decided to prepare and test at first the α-benzyl diol **6.2e**. The (*R*)-enantiomer would give a perfect fit in our active site model, whereas for the (*S*) enantiomer both the phenyl group and the benzyl group fall outside the boundaries of the S and F pocket. Therefore, the chiral recognition for this specific diol is expected to be very high (figure 6.4).
This was indeed observed. Under standard conditions, **6.2e** was resolved by lipase AKG with an enantiomeric ratio of E>100(!). At 50% conversion both the remaining diol and the formed acetate had an e.e. of 95%. Chiral recognition was indeed nearly absolute. By changing the solvent to benzene the resolution could

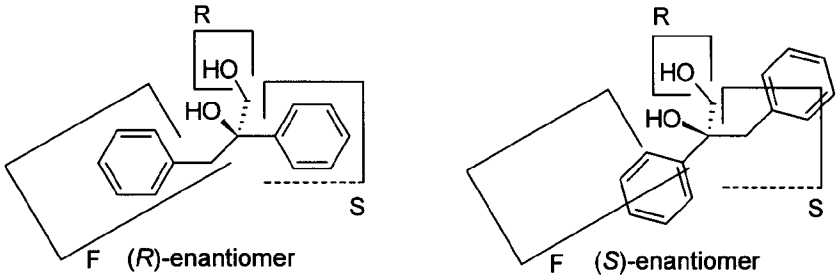



*Figure 6.4 Application of the lipase AKG model to α-benzyl diol* ***6.2e***

even be increased to E > 200 (table 6.10). Under these conditions it is easy to prepare **6.2e** in optically pure form when one goes to a conversion slightly above 50%, as can be seen for the example in hexane. The results from other lipases again show that in those cases chiral discrimination is low. It was now clear that lipase AKG had indeed something special for our substrates.

**Table 6.10. Lipase catalyzed resolution of 6.2e using vinyl acetate**

| lipase | solvent | conversion (%) | e.e. alcohol (%)[a] | e.e. acetate (%) | E |
|---|---|---|---|---|---|
| GC | dipe | 29 | 26 | 64 | 6 |
| CE | dipe | 30 | <2 | <2 | <1 |
| A | dipe | 19 | 10 | 41 | 2.6 |
| HPL | dipe | 38 | 9 | 14 | 1.4 |
| AKG | dipe | 50 | 95 | 95 | >100 |
| AKG | $CHCl_3$ | 28 | 37 | 96 | 70 |
| AKG | hexane | 56 | >98 | 84 | >100 |
| AKG | benzene | 50 | 97 | 97 | >200 |

[a] The e.e. of this alcohol could not be exactly determined by chiral HPLC but was calculated from e.e.(alcohol) = {e.e.(acetate)/conversion -e.e.(acetate)}; the conversion was determined using GC.

Following the same arguments as for **6.2e**, the p-tolyl substituted diol **6.2f** should be recognized as well with high enantiodiscrimination by lipase AKG. Indeed **6.2f** was resolved with an enantiomeric ratio of E ≃ 100 in benzene. At 51% conversion the remaining alcohol had an e.e. of 96% (table 6.11).
The cinnamyl derivative **6.2g** should also be resolved smoothly by lipase AKG according to our model. The unsaturated and flat cinnamyl chain should easily fit in the F pocket, and the phenyl group in the S pocket. Thus again, we expect good

resolution (figure 6.5).

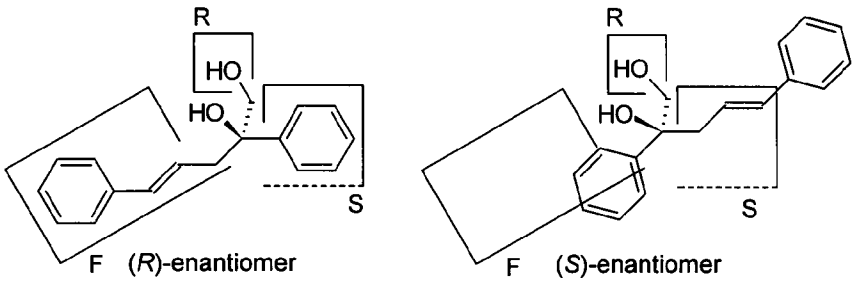



*Figure 6.5 Application of the lipase AKG model to cinnamyl derivative* ***6.2g***

This was indeed the case and an E-factor of 60 in dipe was observed. At 58% conversion the remaining diol **6.2g** had an e.e. of >99%. Catalytic hydrogenation of the double bond of **6.2g** leads to **6.2k** (scheme 6.2). The alkyl chain of this compound is no longer flat and should therefore not be accommodated in the F-pocket. Also a fit of this carbon chain in the S pocket is unlikely due to steric constraints. Chiral recognition should therefore be low. From the result in table 6.11 it is clear that this is indeed the case. All chiral recognition is lost and an enantiomeric ratio of only 2 remains for substrate **6.2k**. Moreover, the overall reactivity decreases.

**Table 6.11. Lipase AKG catalyzed resolution of 6.2g,h and k in benzene using vinyl acetate**

| compound | reaction time (h) | conversion (%) | e.e. alcohol (%) | e.e. acetate (%) | E |
|---|---|---|---|---|---|
| **6.2g** | 42 | 44 | 73 | 92[a] | 60 |
| **6.2g** | 114 | 58 | >99 | 73 | n.d. |
| **6.2k** | 138 | 41 | 19 | 27 | 2 |
| **6.2h** | 114 | 62 | 87 | 54 | 9 |

[a] This acetate could not be resolved by chiral HPLC. Instead, it was isolated by preparative column chromatography and subsequently hydrolyzed to the diol. The e.e. of the diol was then determined by chiral HPLC.

A compound which we expected to be resolved with high chiral discrimination also by lipase AKG due to its flatness is the naphthyl derivative **6.2h**. However, an E-value of only 9 was observed. A closer look at this molecule reveals that this has probably something to do with its geometry (like a *Z*-alkene). We have seen before that *E*-**6.2d** is resolved by lipase AKG with an E-ratio of 16, whereas the *Z*-alkene **6.2d** had an E-ratio of only 4. It can be the case that we now meet the frontiers of our F-pocket and that the *Z*-geometry forces a part of the naphthyl side chain into,

or across, the boundaries of the F-pocket therefore reducing chiral recognition (figure 6.6).

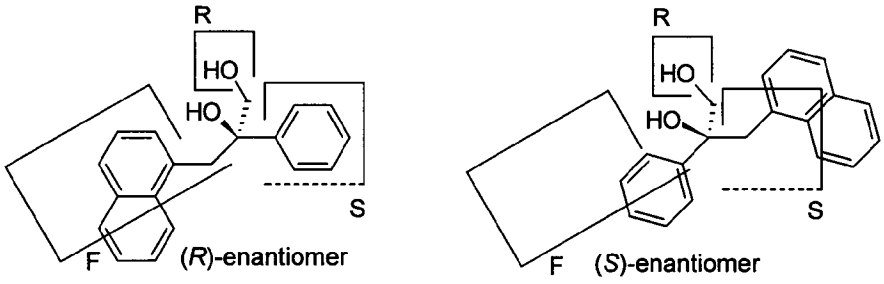
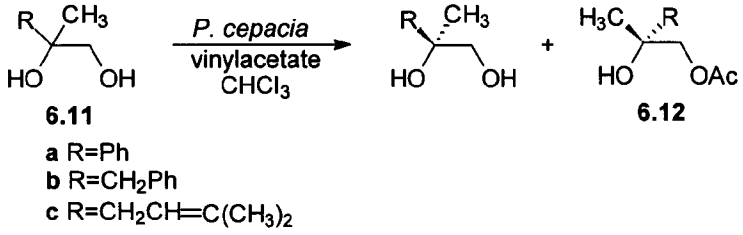



*Figure 6.6 Application of the lipase AKG model to naphthyl derivative **6.2h***

We also prepared diols **6.2j** and **l** but lipase AKG failed to react with these two diols. Some other diols we were interested in testing such as the phenylethyl and the i-amyl derivatives were (as mentioned in section 6.2), unfortunately, not accessible following our synthetic approach.
Recently, an Italian group (Ferraboschi *et al.*) published a paper dealing with the lipase catalyzed resolution of similar diols.[37] They found that lipase from *Pseudomonas cepacia* catalyzed the resolution of **6.11b** and **c** with enantiomeric ratio's of about 20 and 13 respectively. Upon reaction of **6.11a** hardly any chiral recognition took place (scheme 6.10).




**6.11**

**a** R=Ph
**b** R=$CH_2Ph$
**c** R=$CH_2CH{=}C(CH_3)_2$

**6.12**

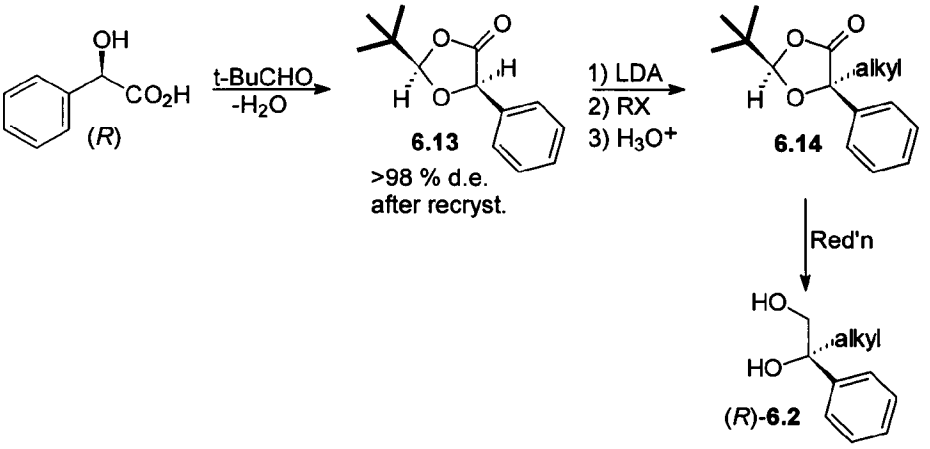
*Scheme 6.10 Resolution of diols **6.11** using P. cepacia lipase*

The authors do not give an explanation for these results, but in our opinion the same arguments can be used as for our resolutions using lipase AKG. It is interesting to note that again a benzyl group and an allylic group give chiral recognition, whereas a phenyl group is insufficient. To check their results, we prepared **6.11b** as well following the strategy of schemes 6.1 and 6.2 in which we used lactic acid instead of mandelic acid as starting material. We found that our *Pseudomonas cepacia* lipase (lipase P, Amano) indeed catalyzed the reaction with an enantiomeric ratio of about 16, which is comparable to the result of Ferraboschi.

Lipase AKG, however, gave only an E-ratio of 9. The fit of the methyl group compared to the phenyl group of **6.2e** in the S-pocket is probably much worse. Similar phenomena of lowering the chiral recognition upon changing a phenyl group for a methyl group have been observed in our research group for the PLE catalyzed hydrolysis of mandelic acids vs. lactic acids.[12]

## 6.11 Determination of the absolute configuration

Although the model which we developed for lipase AKG is crude, it has a predictive value in our series of structural similar diols. Since all these diols have to fit in the same fashion in this model, the stereochemical fate of the reaction would have to be constant throughout the series. This means that all the remaining diols after resolution by lipase AKG should have the same absolute configuration. Our model ,therefore, needs knowledge of the absolute configuration of the diols as a check of its validity. Unfortunately, only the optical rotation of **6.2c** (and corresponding absolute configuration) were known.[9c] After some initial and unsuccessful attempts to establish the absolute configuration of our diols by CD-spectroscopy we decided to prepare the diols in optically pure form by independent asymmetric synthesis, which would also allow determination of the absolute configuration.
As stated in the introductory section 6.1, the most trustworthy route to optically pure diols **6.2** is the Seebach strategy[8] as was employed in the Bayer patent.[7] This method consists of condensation of optically pure mandelic acid with pivalaldehyde with removal of water by azeotropic distillation. A *cis/trans* mixture of dioxolanones in about 90% d.e. is obtained. The major *cis*-dioxolanone **6.13** can be obtained diastereomerically pure by a single crystallization. After generating the enolate with



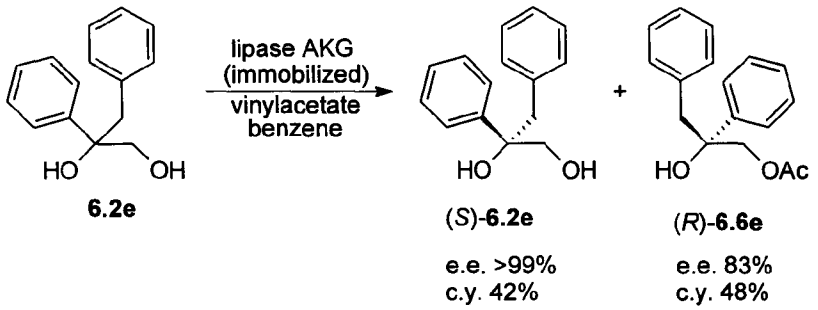

*Scheme 6.11 Synthesis of diols (R)-**6.2** via the 'Seebach' procedure*

LDA the large t-butyl group at the chiral acetal center directs the incoming electrophile to the *trans* position. In this way nearly diastereomerically pure α-alkylated dioxolanones of unambiguous absolute configuration are obtained. Reduction subsequently yields the nearly enantiomerically pure diols **6.2**; the absolute configurations are unambiguous (scheme 6.11).
In this way (*R*)-diols **6.2c,e,f** and **g** were produced from (*R*)-mandelic acid (75-78% yield). Their enantiomeric purity was determined by chiral HPLC; the e.e's varied between 90-95%. It is clear that we can obtain better enantiomeric purities by our enzymatic approach. Subsequently, the retention times of the synthesized diols were compared with samples prepared from lipase AKG catalyzed resolution. In all cases the remaining diol of the resolution had the opposite enantiomeric composition compared to the diols prepared by chemical synthesis. We can conclude that the remaining diols always had the (*S*)-configuration (as had already been determined for **6.2c** by optical rotation) and that the formed acetate therefore must have the (*R*)-configuration. Therefore, we can conclude that the stereochemical outcome of these reactions is constant throughout our series of diols as is predicted by our model.

### 6.12 Immobilization of lipase AKG

As was stated before, all our enzymatic reactions were initially performed on analytical scale (0.3 mmol). Scaling up to a preparative resolution was shown to be difficult due to significant increase of reaction times. The main cause for this increase in (the already long) reaction times was denaturation of the biocatalyst (section 6.5). In the literature, procedures have been described to reduce this denaturation of biocatalysts upon scaling up of reactions. For example, one can covalently bind lipases to polymeric carrier materials,[38] incorporate them into dialysis bags or membranes[39] and even into gels.[40] The most simple procedure is, however, to absorb them onto inert carrier materials such as celite[41] or hyflo super cell.[42] Such an absorption makes the lipase less sensitive to denaturation and therefore increases observed reaction speeds. Absorption takes place by mixing a buffered solution of the lipase and carrier material. After removal of excess water the lipase is absorbed onto the surface. As was discussed in the previous chapter, the lipase retains the conformation and activity corresponding to the pH-buffer from which it is dried. This opens the way to absorb lipase AKG on celite making use of buffers of different pH. According to Amano, lipase AKG is most active between pH 7-10. The pH at which the commercially available lipase AKG is freeze dried is, however, not given. We, therefore, absorbed lipase AKG on celite at a pH of 7 and 8 and compared results. Without immobilization, even after a reaction time of 1 month, a conversion of 50% was never reached. However, by using lipase AKG on celite (pH = 7.00) diol **6.2e** (3 mmol) was converted in 47% yield to the acetate in 3 days. Whereas the E factor for this reaction on analytical scale is $>200$, the immobilized lipase AKG showed an enantiomeric ratio of 'only' 80. The so-obtained

acetate **6.6e** had an enantiomeric excess of 94%. To obtain enantiomerically pure **6.2e** the conversion was allowed to reach 54% (4 days) and the remaining diol was indeed shown to have an enantiomeric purity of >99% (scheme 6.12).




**6.2e**

(*S*)-**6.2e**

e.e. >99%
c.y. 42%

(*R*)-**6.6e**

e.e. 83%
c.y. 48%

*Scheme 6.12 Preparative scale resolution of diol* ***6.2e*** *using immobilized lipase AKG*

Immobilization of lipase AKG at pH = 8.00 gave about the same result. The enantiomeric ratio for this reaction was 64, but the reactivity somewhat decreased. Only after 10 days a conversion of 46% was achieved. Clearly the activity of the at pH 7.00 immobilized lipase AKG is much better.
Also for resolutions of hydroxy-furanones we had very good experiences with immobilizing lipases on inert carriers.[43] The best results for these reactions were, however, obtained using hyflo super cell (HCC) as carrier material. Therefore, we also immobilized lipase AKG on hyflo super cell at pH = 7.00. This immobilization proved to be less fruitfull, as the E for the reaction described above dropped to 32. It is clear from the above described experiments that lipase AKG is definitely stabilized upon absorption on celite and, although we lose some of the chiral recognition, still an excellent enantiomeric ratio of 80 is observed. This immobilization, therefore, opens the way to perform (in the future) resolutions on multi-gram scale.

## 6.13 Conclusions

We have shown that a large variety of tertiary glycols can be easily prepared from α-hydroxy acids such as mandelic acid and lactic acid, making use of simple chemical reagents and transformations. These diols can be regioselectively acylated by a multitude of lipases, of which CAL and CCL are interesting due to their reactivity. Even on several mmol scale, diols **6.2** can be quantitatively acylated on the primary hydroxyl group overnight. Enantioselectivity for these types of acylations are in general, however, low. This is not surprising as reaction takes place relatively far away from the chiral center. Only lipase AKG is capable of giving good chiral discrimination for a specific range of unsaturated substrates.

Based on this series of substrates we have devised an active site model for lipase AKG, which seems to have a predictive value for this type of diols. Although there is no actual 3D-structure available for our lipase, by comparison of our model with the structure of another *Pseudomonas* lipase we have shown that there might be an actual physical basis for our model. By independent synthesis we have shown that the enantiomeric preference of lipase AKG throughout the series of diols is constant, as is expected from our primitive model. Scaling our reactions up from 0.3 mmol to 3 mmol has proven to be successful as well. Reactivity can be enhanced significantly by immobilization of lipase AKG on celite but it goes with some loss in chiral discrimination.

## 6.14 Experimental

For general remarks see chapter 2.

**General procedure for the α-alkylation of dioxolanone 6.4**
In an atmosphere of nitrogen, using predried glassware, diisopropylamine (3.50 ml, 25 mmol) was dissolved in 50 ml of dry THF. After cooling to -80 °C, n-Buli (14 ml, 1.6 N in hexane, 22 mmol) was added. The mixture was stirred for 15 min and recooled to -80 °C. Dioxolanone **6.4**[12] (3.84 g, 20 mmol) was dissolved in 20 ml of dry THF and added dropwise to the LDA-solution. After stirring for another 15 min the yellow enolate solution was cooled to -80 °C and a solution of the alkyl halide (22 mmol) in 10 ml of THF was added dropwise. Under stirring, the reaction mixture was slowly allowed to reach room temperature (approx. 3h) and quenched with a saturated $NH_4Cl$ solution. The reaction mixture was extracted three times with ether (100 ml) and the combined organic layers were washed with brine. After drying ($Na_2SO_4$) and evaporation there remained a near quantitative yield of the α-alkylated dioxolanone **6.5** which can be purified as described by Moorlag.[12] Generally, however, the purity was checked by $^1$H-NMR and crude **6.5** was directly reduced to the corresponding diol **6.2**.

**General procedure for the reduction of α-alkylated dioxolanones 6.5 to diols 6.2**
In an atmosphere of nitrogen, using predried glassware, $LiAlH_4$ (2.28 g, 60 mmol) was suspended in 100 ml of dry THF. Slowly a solution of **6.5** (20 mmol) in 25 ml of dry THF was added under stirring. The solution was refluxed for 2 h and after cooling to room temperature excess $LiAlH_4$ was carefully destroyed using a saturated $NH_4Cl$ solution. The reaction mixture was filtered over celite which was washed with 200 ml of ether. The combined organic layers were washed with brine and dried ($Na_2SO_4$). After evaporation crude **6.2** was obtained which was purified as indicated.

**2-Phenylbutane-1,2-diol (6.2a)**
Starting from **6.4** and ethyl iodide, following the procedures described above, there

was obtained **6.2a** (2.77 g, 16.7 mmol, 83%) after bulb to bulb distillation (95 °C/ 0.07 mm Hg) as a colorless oil which solidified upon standing; mp 52.6-54.5 °C (lit.,[44] mp 56 °C); $^1$H-NMR ($CDCl_3$): $\delta$ 0.77 (t, J = 6 Hz, 3H), 1.84 (m, 2H), 1.95 (br, 1H), 2.73 (s, 1H), 3.65 (dd, J = 6 Hz, $J_{AB}$ = 11 Hz, 1H), 3.85 (d, $J_{AB}$ = 11 Hz, 1H), 7.27-7.44 (m, 5H); $^{13}$C-NMR ($CDCl_3$): $\delta$ 7.38 (q), 31.09 (t), 70.35 (t), 77.48 (s), 125.59 (d), 126.97 (d), 128.33 (d), 143.70 (s); Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.25; H, 8.49. Found: C, 72.54; H, 8.47. HRMS calcd m/z 166.099. Found 166.099.

**2-Phenylpentane-1.2-diol (6.2b)**
Starting from **6.4** and n-propyl iodide, following the procedures described above, there was obtained **6.2b** (1.94 g, 10.8 mmol, 52%) after bulb to bulb distillation (115 °C/ 0.2 mm Hg) as a colorless oil; $^1$H-NMR ($CDCl_3$): $\delta$ 0.85 (t, J = 7.2 Hz, 3H), 0.95-1.45 (m, 2H), 1.76 (m, 2H), 2.08 (br, 1H), 2.83 (br, 1H), 3.66 (d, $J_{AB}$ = 11 Hz), 3.82 (d, $J_{AB}$ = 11 Hz), 7.20-7.45 (m, 5H); $^{13}$C-NMR ($CDCl_3$): $\delta$ 14.40 (q), 16.38 (t), 40.81 (t), 70.51 (t), 77.22 (s), 125.47 (d), 126.92 (d), 128.32 (d), 143.80 (s); HRMS calcd m/z 180.115. Found 180.115. Due to the hygroscopic character of this compound a correct elemental analysis could not be obtained.[45]

**2-Phenylpent-4-ene-1,2-diol (6.2c)**
Starting from **6.4** (50 mmol) and allyl bromide (55 mmol), following the procedures described above, there was obtained **6.2c** (6.45 g, 36.2 mmol, 73%) as a colorless oil after bulb to bulb distillation (115 °C/ 0.01 mm Hg); $^1$H-NMR ($CDCl_3$): $\delta$ 1.92 (dd, J = 8.0 Hz and J = 5.1Hz, 1H), 2.58-2.80 (m, 3H), 3.65-3.84 (m, 2H), 5.09-5.21 (m, 2H), 5.51-5.69 (m, 1H), 7.25-7.47 (m, 5H); $^{13}$C-NMR ($CDCl_3$): $\delta$ 42.90 (t), 70.03 (t), 76.34 (s), 119.63 (t), 125.41 (d), 127.19 (d), 128.39 (d), 132.83 (d), 143.76 (s); HRMS calcd m/z (- $H_2O$) 160.089. Found 160.089. Due to the hygroscopic character of this compound a correct elemental analysis could not be obtained.[45]

**2-Phenylhex-4-ene-1,2-diol (6.2d)**
Starting from **6.4** and *E/Z*-crotyl bromide, following the procedures described above, there was obtained **6.2d** (2.40 g, 12.5 mmol, 60%) as a colorless oil after bulb to bulb distillation (120 °C/ 0.08 mm Hg); 1.61 and 1.65 (s, 3H), 2.38-2.87 (m, 4H), 3.59-3.77 (m, 3H), 5.12-5.29 (m, 1H), 5.49-5.66 (m, 1H), 7.22-7.46 (m, 5H); $^{13}$C-NMR ($CDCl_3$): $\delta$ 17.98 (q), 41.60 (t), 69.88 (t), 76.32 (s), 124.97 (d), 125.51 (d), 127.01 (d), 128.27 (d), 130.57 (d), 143.91 (s); HRMS calcd m/z (- $H_2O$) 174.104. Found 174.104. Due to the hygroscopic character of this compound a correct elemental analysis could not be obtained.[45]

**2,3-Diphenylpropane-1,2-diol (6.2e)**
Starting from **6.4** (18 mmol) and benzyl bromide, following the procedures described above, there was obtained **6.2e** (3.77 g, 16.5 mmol, 92%) as a white solid. Recrystalization from EtOAc/hexane afforded tiny white needles of pure **6.2e**; mp 75.2-75.7°C (lit.,[46] 73°C); $^1$H-NMR ($CDCl_3$): $\delta$ 2.08 (br, 1H), 2.61 (br, 1H), 3.17 (dd, $J_{AB}$ = 14 Hz, 2H), 3.77 (d, $J_{AB}$ = 11Hz, 1H), 3.87 (d, $J_{AB}$ = 11 Hz, 1H), 6.92-6.97 (m, 2H), 7.18-7.36 (m, 8H); $^{13}$C-NMR ($CDCl_3$): $\delta$ 44.87 (t), 69.28 (t), 77.04 (s), 125.06 (d), 126.70 (d), 127.17 (d), 128.08 (d), 128.25 (d), 130.52 (d), 135.76 (s), 143.20 (s).

**2-Phenyl-3-p-tolylpropane-1,2-diol (6.2f)**
Starting from **6.4** and $\alpha$-bromoxylene, following the procedure described above, **6.5f** was obtained as a yellow oil which was bulb to bulb distilled (150 °C/ 0.01 mm Hg) to yield **6.5f** (5.65 g, 19.1 mmol, 95%) contaminated with a small trace of $\alpha$-bromo-xylene. Subsequently 17 mmol **6.5f** was reduced following the standard procedure to yield a white solid which was recrystallized from EtOAc/hexane to give pure **6.2f** (3.31 g, 13.7 mmol, 81%) as white needles; mp 91.5-91.7°C; $^1$H-NMR ($CDCl_3$): $\delta$ 1.84 (br, 1H), 2.28 (s, 3H), 2.46 (s, 1H), 3.15 (dd, $J_{AB}$ = 15 Hz, 2H), 3.82 (dd, $J_{AB}$ = 12 Hz, 2H), 6.84 (d, J = 8 Hz, 2H), 7.01 (d, J = 8 Hz, 2H), 7.05-7.39 (m, 5H); $^{13}$C-NMR ($CDCl_3$): $\delta$ 21.01 (q), 44.15 (t), 68.99 (t), 76.91 (s), 125.45 (d), 126.93 (d), 127.98 (d), 128.51 (d), 130.08 (d), 132.24 (s), 135.88 (s), 143.25 (s); Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.18; H, 7.49. HRMS calcd m/z (-$H_2O$) 224.120. Found 224.120.

**2,5-Diphenylpent-4-ene-1,2-diol (6.2g)**
Dioxolanone **6.5g**[12] (920 mg, 2.98 mmol) was dissolved in 12 ml of t-BuOH and $NaBH_4$ (285 mg, 7.5 mmol) was added. The mixture was brought to reflux and 2.4 ml of MeOH was added in small portions over a period of 1h. After refluxing for another h, water was added and the solution partially evaporated at reduced pressure. The remaining water layer was extracted twice with ethyl acetate, The combined organic layers were washed with brine and after drying ($Na_2SO_4$) evaporated to dryness. As determined from the 200 MHz $^1$H-NMR spectrum this residue consisted for 85% of product and 15% of starting material. Pure **6.2g** (430 mg, 1.69 mmol, 67%) was isolated by column chromatography (silica, ether/hexane 1:2) as a colorless oil which solidified upon standing; mp 70.0-71.5 °C; $^1$H-NMR ($CDCl_3$): $\delta$ 2.12 (br, 1H), 2.84 (m, 3H), 3.81 ($br_{AB}$, 2H), 6.01(m, 1H), 6.50 (d, J = 16 Hz, 1H), 7.20-7.50 (m, 10H); $^{13}$C-NMR ($CDCl_3$): $\delta$ 42.23 (t), 69.93 (t), 76.66 (s), 124.16 (d), 125.44 (d), 126.17 (d), 127.25 (d), 127.41 (d), 128.47 (d), 134.45 (d), 136.90 (s), 143.24 (s); Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.04; H, 7.17. HRMS calcd m/z (-$H_2O$) 206.120. Found 206.120.

**3-Naphthalene-1-yl-2-phenylpropane-1,2-diol (6.2h)**
Following the procedure described above the lithium enolate from **6.4** (20 mmol) was generated. To this solution was added freshly distilled 1-chloromethylnaphthalene (3.88 g, 22 mmol) in dry THF. After stirring at room temperature overnight, saturated $NH_4Cl$ solution was added and the mixture was extracted three times with ether. The organic layers were washed with brine and after drying ($Na_2SO_4$) evaporated. There remained 6.98 g of material composed of **6.4**, **6.5h** and alkyl halide. Excess alkyl halide and **6.4** were distilled of in a kugelrohr apparatus (80 °C/ 0.01 mm) and the remaining yellow oil was filtered over silica using hexane/EtOAc 9:1. The crude **6.5h** obtained this way was reduced using $LiAlH_4$ (700 mg) following the standard procedure. After work-up a yellow oil was obtained which was purified by column chromatography (silica/ether) to give **6.2h** (1.18 g, 4.24 mmol, 21%) as a colorless solid. For analytical purposes a small portion was recrystallized from EtOAc/hexane to give tiny white needles; mp 73.5-74.5 °C; $^1$H-NMR ($CDCl_3$): $\delta$ 1.85 (br, 1H), 2.52 (s, 1H), 3.50 (d, $J_{AB}$ = 14 Hz, 1H), 3.81 (d, $J_{AB}$ = 14 Hz, 1H), 3.88 (m, 2H), 7.09 (d, J = 6 Hz, 1H), 7.20-7.47 (m, 8H), 7.67-7.86 (m, 2H), 8.00-8.09 (m, 1H); $^{13}$C-NMR ($CDCl_3$): $\delta$ 41.08 (t), 69.09 (t), 77.42 (s), 124.03 (d), 124.82 (d), 125.34 (d), 125.61 (d), 126.92 (d), 127.29 (d), 127.98 (d), 128.40 (d), 128.92 (d), 131.93 (s), 132.72 (s), 133.66 (s), 143.35 (s); Anal. Calcd for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52. Found: C, 81.10; H, 6.55; HRMS calcd m/z 278.131. Found 278.131.

**1-Cyclohexyl-1-phenylethane-1,2-diol (6.2j)**
Starting from **6.4** (40 mmol) and 3-bromo-cyclohexene,[47] following the procedures described above there was obtained **6.2i** (5.56 g, 25.5 mmol, 64%) as a mixture of two diastereomers which was purified by bulb to bulb distillation (110 °C/ 0.01 mm Hg). Diol **6.2i** (900 mg, 4.13 mmol) was dissolved in 100 ml of MeOH. A catalytic amount of Pd/C (10%) was added and the mixture was hydrogenated overnight in a parr apparatus. After filtration the mixture was evaporated to dryness to give a quantative yield of **6.2** j; mp 85 °C (lit.,[48] 86-88 °C (for the (*S*)-enantiomer)); $^1$H-NMR ($CDCl_3$): $\delta$ 0.80-1.93 (m, 12H), 2.70 (br, 1H), 3.83 (d, $J_{AB}$ = 11 Hz, 1H), 3.99 (d, $J_{AB}$ = 11 Hz, 1H), 7.14-7.53 (m, 5H); $^{13}$C-NMR ($CDCl_3$): $\delta$ 26.27 (t), 26.43 (t), 26.56 (t), 26.78 (t), 27.16 (t), 45.50 (d), 68.07 (t), 126.14 (d), 126.87 (d), 128.11 (d).

**2,5-Diphenylpentane-1,2-diol (6.2k)**
Starting from **6.5g** (10 mmol) following the procedure described above using $LiAlH_4$ there was obtained a mixture of **6.2g** and **6.2k**. This mixture was dissolved in 50 ml of MeOH and hydrogenated in a Parr apparatus overnight in the presence of a catalytic amount Pd/C (10%). After filtration **6.2k** was obtained which was purified by column chromatography (silica/ ether) to give pure material (1.82 g, 7.11 mmol, 71%) as a colorless oil which solidified upon standing; mp 63.1-64 °C; $^1$H-NMR ($CDCl_3$): $\delta$ 1.34-1.88 (m, 4H), 2.44 (br, 2H), 2.49-2.61 (m, 2H), 3.63 (d, $J_{AB}$ =

11 Hz, 1H), 3.78 (d, $J_{AB}$ = 11 Hz, 1H), 7.09-7.38 (m, 10H); $^{13}$C-NMR ($CDCl_3$): $\delta$ 24.72 (t), 36.01 (t), 37.96 (t), 70.58 (t), 77.17 (s), 125.50 (d), 125.73 (d), 127.00 (d), 128.24 (d), 128.38 (d), 141.84 (s), 143.15 (s); Anal. Calcd for $C_{17}H_{20}O_2$; C, 79.65; H, 7.86. Found; C, 79.42; H, 7.90; HRMS calcd (-$H_2O$) m/z 238.136. Found 238.136.

**2,3-Dihydroxy-1,2-diphenylpropane-1-one (6.2l)**
This compound was prepared from benzoin and paraformaldehyde following a literature procedure.[49]

**4-Bromomandelic acid (6.7a)**
Starting from *p*-bromoacetophenone (0.25 mol), **6.7a** (25.17 g, 0.11 mol, 44%) was obtained as colorless needles following a literature procedure;[28] mp 117.8-119.0 (lit.,[28] 117-119°C).

**4-Methoxymandelic acid (6.7b)**
Starting from *p*-methoxyacetophenone (59.4 g, 0.396 mol), **6.7b** (36.0 g, 0.20 mol, 51%) was obtained as colorless needles after recrystalization from ether/toluene 1:4 following a procedure analogous to **6.7a**; mp 107.8-108.2°C (lit.,[50] 108°C).

**4-Fluoromandelic acid (6.7c)**
Starting from *p*-fluoroacetophenone (28.4 g, 0.206 mol), **6.7c** (22.18 g, 0.130 mol, 63%) was obtained as an off-white powder after recrystalization from benzene following a literature procedure[51] analogous to **6.7a**. mp 135.3-136.2°C (lit.,[51] not given).

**5-(4-Bromo-phenyl)-2,2-dimethyl-[1,3]dioxolane-4-one (6.8a)**
A mixture of **6.7a** (20.0 g, 86.6 mmol) and acetone (25 g) in 100 ml of benzene containing a catalytic amount of $H_2SO_4$ was azeotropically refluxed for 8 h. After cooling, the mixture was washed three times with a saturated $NaHCO_3$ solution followed by brine. After drying ($Na_2SO_4$) the solution was evaporated to dryness to yield **6.8a** (13.24 g, 48.9 mmol, 57%); mp 62.0-63.0 (lit.,[52] 65-66°C); $^1$H-NMR ($CDCl_3$): $\delta$ 1.66 (s, 3H), 1.71 (s, 3H), 5.34 (s, 1H), 7.33-7.37 (m, 2H), 7.50-7.56 (m, 2H); $^{13}$C-NMR ($CDCl_3$): $\delta$ 26.07 (q), 27.19 (q), 75.09 (d), 111.13 (s), 122.82 (s), 127.93 (d), 131.82 (d), 133.52 (s), 172.06 (s).

**5-(4-Methoxy-phenyl)-2,2-dimethyl-[1,3]dioxolane-4-one (6.8b)**
Following the same procedure as for **6.4** there was obtained from **6.7b** (20.0 g, 0.11 mol) and dimethoxypropane (13.5 g, 0.13 mol) a quantitative yield of **6.8b** (24.4 g, 0.11 mol) as an oil which solidified upon standing; mp 35-36°C; $^1$H-NMR ($CDCl_3$): $\delta$ 1.65 (s, 3H), 1.71 (s, 3H), 3,79 (s, 3H), 5.34 (s, 1H), 6.91-6.95 (m, 2H), 7.34-7.38 (m, 2H); $^{13}$C-NMR ($CDCl_3$): $\delta$ 25.95 (q), 27.19 (q), 55.26 (q),

75.75 (d), 110.62 (s), 114.17 (d), 126.67 (s), 128.13 (d), 160.06 (s), 171.45 (s).

**5-(4-Fluoro-phenyl)-2,2-dimethyl-[1,3]dioxolane-4-one (6.8c)**
Following the same procedure as for **6.4** there was obtained from **6.7c** (20.0 g, 117 mmol) and dimethoxypropane (15.6 g, 150 mmol) **6.8c** (22.59 g, 108 mmol, 92%) after recrystalization from ether/hexane; mp 71.0-71.2 °C; $^1$H-NMR ($CDCl_3$): $\delta$ 1.68 (s, 3H), 1.72 (s, 3H), 5.37 (s, 1H), 7.06-7.16 (m, 2H), 7.42-7.49 (m, 2H); $^{13}$C-NMR ($CDCl_3$): $\delta$ 26.05 (q), 27.20 (q), 75.22 (d), 110.97 (s), 115.50 (d), 115.94 (d), 128.14 (d), 128.31 (d), 161.13 (s), 164.83 (s); $^{19}$F-NMR ($CDCl_3$): $\delta$ 165.22; Anal. Calcd for $C_{11}H_{11}FO_3$: C, 62.85; H, 5.27; F, 9.04. Found: C, 62.61; H, 5.40, F, 9.04. HRMS calcd m/z 210.069. Found 210.069.

**5-(4-Chloro-phenyl)-2,2-dimethyl-[1,3]dioxolane-4-one (6.8d)**
Following the same procedure as for **6.4** there was obtained from **6.7d** (10.0 g, 53.6 mmol) and dimethoxypropane (6.76 g, 65 mmol) **6.8d** (10.07 g, 44.5 mmol, 83%) after recrystalization from ether/hexane; mp 67-68 °C and 72-73 °C; $^1$H-NMR ($CDCl_3$): $\delta$ 1.68 (s, 3H), 1.72 (s, 3H), 5.37 (s, 1H), 7.35-7.47 (m, 5H); $^{13}$C-NMR ($CDCl_3$): $\delta$ 26.08 (q), 27.19 (q), 75.14 (d), 111.16 (s), 127.60 (d), 128.90 (d), 132.87 (s); Anal. Calcd for $C_{11}H_{11}ClO_3$: C, 58.29, H, 4.89, Cl, 15.64. Found: C, 58.07, H, 4.92, Cl, 15.82.

**2-(4-Bromo-phenyl)pent-4-ene-1,2-diol (6.9a)**
Following the same procedures as for diols **6.2** there was obtained from **6.8a** (5.00 g, 18.4 mmol) and allyl bromide, **6.9a** (3.87 g, 15.0 mmol, 82%). An analytical sample was prepared by recrystalization from benzene/hexane; mp 62.0-62.5 °C; $^1$H-NMR ($CDCl_3$): $\delta$ 2.37 (br, 2H), 2.60 (s, 1H), 2.64 (s, 1H), 3.66 (d, $J_{AB}$ = 11.3 Hz), 3.74 (d, $J_{AB}$ = 11.3 Hz), 5.14-5.17 (m, 2H), 5.47-5.68 (m, 1H), 7.27-7.33 (m, 2H), 7.46-7.53 (m, 2H); $^{13}$C-NMR ($CDCl_3$): $\delta$ 42.81 (t), 69.75 (t), 76.00 (s), 119.98 (s), 127.37 (d), 131.44 (d), 132.37 (d), 142.39 (s); Anal. Calcd for $C_{11}H_{13}BrO_2$: C, 51.38; H, 5.10; Br, 31.08. Found: C, 51.50, H, 5.08, Br, 31.13. HRMS calcd m/z (-$H_2O$) 237.999. Found 237.999.

**2-(4-Methoxy-phenyl)pent-4-ene-1,2-diol (6.9b)**
Following the same procedures as for diols **6.2** there was obtained from **6.8b** (4.11 g, 18.5 mmol) and allyl bromide after bulb to bulb distillation (200 °C/ 2 mm Hg) pure **6.9b** as a colorless oil (3.25 g, 15.6 mmol, 84%); $^1$H-NMR ($CDCl_3$): $\delta$ 1.86 (dd, J = 8.1 Hz and J = 5.1 Hz, 1H), 2.56 (s, 1H), 3.62-3.78 (m, 2H), 3.82 (s, 3H), 5.09-5.19 (m, 2H), 5.52-5.65 (m, 1H), 6.87-6.95 (m, 2H), 7.27-7.38 (m, 2H); $^{13}$C-NMR ($CDCl_3$): $\delta$ 43.03 (t), 55.27 (q), 70.22 (t), 113.68 (d), 119.51 (s), 126.67 (d), 133.03 (d). HRMS calcd m/z (-$H_2O$) 190.099. Found 190.099. Due to the hygroscopic character of this compound no correct elemental analysis could be obtained.[45]

**2-(4-Fluoro-phenyl)pent-4-ene-1,2-diol (6.9c)**
Following the same procedure as for diols **6.2** there was obtained from **6.8c** (4.20 g, 20 mmol) the $\alpha$-allylated dioxolanone (4.04 g, 16.2 mmol, 81%) which was purified by bulb to bulb distillation (90 °C/ 1 mm Hg). This intermediate (10 mmol) was subsequently reduced to give after bulb to bulb distillation (105 °C/ 0.05 mm Hg) **6.9c** (1.76 g, 8.98 mmol, 90%) as a colorless oil; $^1$H-NMR ($CDCl_3$): $\delta$ 2.06 (br, 1H), 2.55-2.72 (m, 3H), 3.67 (d, $J_{AB}$ = 11.1 Hz, 1H), 3.75 (d, $J_{AB}$ = 11.1 Hz, 1H), 5.09-5.18 (m, 2H), 5.49-5.70 (m, 1H), 7.01-7.11 (m, 2H), 7.27-7.45 (m, 3H); $^{13}$C-NMR ($CDCl_3$): $\delta$ 42.96 (t), 69.93 (t), 75.90 (s), 114.94 (d), 115.35 (d), 119,83 (s), 127.12 (d), 127.28 (d), 132.55 (d); HRMS calcd m/z (-$H_2O$) 178.079. Found 178.079. Due to the hygroscopic character of this compound a correct elemental analysis could not be obtained.[45]

**2-(4-Chloro-phenyl)pent-4-ene-1,2-diol (6.9d)**
Following the same procedure as for diols **6.2** there was obtained from **6.8d** (4.53 g, 20 mmol) and allyl bromide, **6.9c** (3.30 g, 15.5 mmol, 78%) which was purified by bulb to bulb distillation (160/ 0.05 mm Hg); $^1$H-NMR ($CDCl_3$): $\delta$ 1.93 (br, 1H), 2.62-2.66 (m, 3H), 3.72 (m, 2H), 5.10-5.18 (m, 2H), 5.48-5.66 (m, 1H), 7.27-7.40 (m, 5H); 42.85 (t), 69.85 (t), 76.35 (s), 119,99 (s), 126.97 (d), 128.49 (d), 132.40 (d), 141.88 (s); HRMS calcd m/z (-$H_2O$) 194.050. Found 194.050. Due to the hygroscopic character of this compound a correct elemental analysis could not be obtained.[45]

**2-Methyl-3-phenylpropane-1,2-diol (6.11b)**
The dioxolanone (2.60 g, 20 mmol) derived from lactic acid was $\alpha$-benzylated using the standard procedure to give the $\alpha$-alkylated product (3.67 g, 16.7 mmol, 83%) after bulb to bulb distillation (105 °C/ 0.5 mm Hg). This compound (10 mmol) was reduced with $LiAlH_4$ (30 mmol) to give crude **6.11 b** (1.12 g, 0.67 mmol, 67%) which was purified by column chromatography (silica, ether); mp 53.6-54.3 °C (lit.,[53] 55-56 °C).

**General procedure for the enzymatic conversion of diols 6.2 to their corresponding mono acetates**
Diol **6.2** (1.0 mmol) was dissolved in 3 ml of dipe and 0.5 ml of vinyl acetate. Candida antarctica (25 mg) was added and the mixture was stirred at room temperature. Conversion was monitored by TLC (silica ether/hexane 1:2). At 100 % conversion the enzyme was filtered off and washed with ether. The filtrate was evaporated to give a quantitave yield of monoacetate which was purified by column chromatography (silica, ether/hexane 1:2).

**Acetic acid 2-hydroxy-2-phenylbutyl ester (6.6a)**
$^1$H-NMR ($CDCl_3$): $\delta$ 0.77 (t, J = 7.4 Hz, 3H), 1.81-1.98 (dq, J = 7.5 Hz, $J_{AB}$ = 1.5 Hz, 2H), 2.01 (s, 3H), 4.26 (d, $J_{AB}$ = 11.4 Hz, 1H), 4.31 (d, $J_{AB}$ = 11.4 Hz,

1H), 7.22-7.44 (m, 5H); $^{13}$C-NMR ($CDCl_3$): $\delta$ 7.33 (q), 20.67 (q), 31.25 (t), 76.10 (s), 125.44 (d), 127.03 (d), 128.17 (d), 142.94 (s); Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21, H, 7.74. Found: C, 68.63, H, 7.72. HRMS calcd m/z 208.110. Found 208.110.

**Acetic acid 2-hydroxy-2-phenylpentyl ester (6.6b)**
$^1$H-NMR ($CDCl_3$): $\delta$ 0.85 (t, J = 7.1 Hz, 3H), 1.07-1.32 (m, 2H), 1.76-1.98 (m, 2H), 2.01 (s, 3H), 4.25 (d, $J_{AB}$ = 11.5, 1H), 4.36 (d, $J_{AB}$ = 11.5, 1H), 7.25-7.44 (m, 5H); $^{13}$C-NMR ($CDCl_3$): $\delta$ 14.32 (q), 16.34 (t), 20.93 (q), 41.31 (t), 71.40 (t), 75.96 (t), 125.31 (d), 127.00 (d), 128.17 (d), 143.41 (s); Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.44; H, 8.11. HRMS calcd m/z 222.126. Found 222.126.

**Acetic acid 2-hydroxy-2-phenylpent-4-enyl ester (6.6c)**
$^1$H-NMR ($CDCl_3$): $\delta$ 2.02 (s, 3H), 2.62-2.69 (m, 3H), 4.27 (d, $J_{AB}$ = 11.5 Hz), 4.35 (d, $J_{AB}$ = 11.5 Hz), 5.12-5.16 (m, 2H), 5.50-5.72 (m, 1H), 7.27-7.47 (m, 5H); $^{13}$C-NMR ($CDCl_3$): $\delta$ 20.59 (q), 43.60 (t), 70.62 (s), 119.64 (t), 125.44 (d), 127.27 9d), 128.24 (d), 132.36 (d), 142.56 (s), 171.07 (s); Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89, H, 7.32. Found: C, 70.60, H, 7.33. HRMS calcd m/z 220.110. Found 220.110.

**Acetic acid 2-hydroxy-3-phenylhex-4-enyl ester (6.6d)**
$^1$H-NMR ($CDCl_3$) (major isomer): $\delta$ 1.62 (d, J = 6.6 Hz, 3H), 2.02 (s, 3H), 2.47-2.69 (m, 3H), 4.23 (d, $J_{AB}$ = 11.4 Hz, 1H), 4.33 (d, $J_{AB}$ = 11.4 Hz, 1H), 5.11-5.29 (m, 1H), 5.48-5.63 (m, 1H), 7.23-7.47 (m, 5H); $^{13}$C-NMR ($CDCl_3$) (major isomer): $\delta$ 18.05 (q), 20.81 (q), 42.33 (t), 70.55 (t), 74.95 (s), 124.43 (d), 125.47 (d), 127.16 (d), 128.18 (d), 130.82 (d), 142.95 (s); Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.00; H, 7.77. HRMS calcd m/z (-$H_2O$) 216.115. Found 216.115.

**Acetic acid 2-hydroxy-2,3-diphenylpropyl ester (6.6e)**
$^1$H-NMR ($CDCl_3$): $\delta$ 2.01 (s, 3H), 2.53 (br, 1H), 3.16 (dd, $J_{AB}$ = 13.8 Hz, 2H), 4.31 (d, $J_{AB}$ = 11.4 Hz, 1H), 4.46 (d, $J_{AB}$ = 11.4 Hz, 1H), 6.95-7.00 (m, 2H), 7.18-7.37 (m, 8H); $^{13}$C-NMR ($CDCl_3$): $\delta$ 20.54 (q), 45.85 (t), 70.03 (t), 75.71 (t), 125.54 (d), 126.77 (d), 127.26 (d), 128.09 (d), 130.55 (d), 135.37 (s), 142.72 (s); mp 41.6-42.3°C; Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.41; H, 6.77; HRMS calcd m/z 270.126. Found 270.126.

**General procedure for the enzymatic resolutions of diols 6.2 and 6.9**
Diol (0.25 mmol) was dissolved in 1 ml of solvent and 0.3 ml of vinyl acetate. Lipase (20 mg) was added and the heterogeneous mixture was stirred at room temperature. The progress of the reaction was monitored by TLC (silica ether/hexane 1:2, staining alkaline $KMnO_4$ or phosphomolybdic acid in EtOH). At

regular intervals aliquots of 0.1 ml were taken which were filtered over 0.5 cm celite in a pasteur pipette. The celite was washed with 1 ml of $CH_2Cl_2$ and the filtrate was evaporated. The residue was dissolved in 1 ml of i-PrOH and analyzed on a chiral Daicel OJ HPLC column as indicated in appendix A. If the e.e's of both components could not be detected in a single run, the components were separated by preparative TLC.

**General procedure for the diastereoselective synthesis of (*R*)-diols 6.2**

*Cis*-dioxolanone **6.13** was prepared from (*R*)-mandelic acid and pivalaldehyde as described by Seebach.[8] In an atmosphere of nitrogen using predried glassware diisopropylamine (1.26 ml, 9 mmol) was dissolved in 50 ml of dry THF. After cooling to -80 °C n-Buli (5.2 ml, 1.6 N in hexane, 8.2 mmol) was added. The mixture was stirred for 15 min and recooled to -80 °C. Dioxolanone **6.13** (1.65 g, 7.5 mmol) was dissolved in 10 ml of dry THF and added dropwise to the LDA-solution. After stirring for another 30 min the yellow enolate solution was cooled to -80 °C, and a solution of the alkyl halide (8 mmol) in 10 ml of THF was added dropwise. Under stirring the reaction mixture was slowly allowed to reach room temperature (approx. 5h) and quenched with a saturated $NH_4Cl$ solution. The reaction mixture was extracted three times with ether (100 ml) and the combined organic layers were washed with brine. After drying ($Na_2SO_4$) and evaporation, there remained a near quantitative yield of the $\alpha$-alkylated dioxolanone **6.14**. The purity was checked by $^1$H-NMR and **6.14** was subsequently reduced to the corresponding (*R*)-diol **6.2** by slowly adding a solution in dry THF to $LiAlH_4$ (816 mg, 21 mmol) in 100 ml of THF under inert conditions. After reflux for 2h, excess hydride was destroyed by the careful addition of saturated $NH_4Cl$ solution. The mixture was filtered over celite which was washed with 200 ml of ether. The filtrate was washed with brine and dried ($Na_2SO_4$) to give the crude, enantiomerically enriched, diol **6.2** after evaporation. The diol was purified as described and its enantiomeric composition determined by chiral HPLC (OJ) as indicated in appendix A.

**(*R*)-2-Phenylpent-4-ene-1,2-diol (6.2c)**

This compound was purified by column chromatography (silica, ether/hexane 1:2) to give pure (*R*)-**6.2c** (1.01 g, 5.67 mmol, 76%) as a colorless oil; NMR-spectra in accordance with it's racemate; e.e. 92 %; $[\alpha]_D^{25}$ + 47° (c, 1.24 in $CHCl_3$) (lit.,[9] $[\alpha]_D^{25}$ + 49.5°); o.p. 95%.

**(*R*)-2,3-Diphenylpropane-1,2-diol (6.2e)**

This compound was purified by crystallization from ether/hexane to provide (*R*)-**6.2e** (1.34 g, 5.88 mmol, 78%) as a white solid; mp 62.2-63.2°C (lit.,[7] 62°C); NMR-spectra in accordance with it's racemate; e.e. 94% (determined as the mono acetate, prepared via CAL acylation); $[\alpha]_D^{25}$ = + 76.5° (c, 1.44 in $CHCl_3$).

**(*R*)-2-Phenyl-3-p-tolylpropane-1,2-diol (6.2f)**
This compound was purified by recrystalization from ether/hexane to give pure (*R*)-**6.2f** (1.40g, 5.78 mmol, 77%) as a white solid; mp 83.8-84.2°C; NMR-spectra in accordance with it's racemate; e.e. 93%; $[\alpha]_D^{25}$ = + 84.8° (c, 1.12 in $CHCl_3$).

**(*R*)-2,5-Diphenylpent-4-ene-1,2-diol (6.2g)**
This compound was prepared via reduction of 3.5 mmol α-alkylated dioxolanone using $NaBH_4$ (as for the racemate) to give pure (*R*)-**6.2g** (670 mg, 2.64 mmol, 75%) after column chromatography (silica, ether/hexane 1:1) as a colorless oil which solidified on prolonged standing; mp 49.6-50.2°C; NMR-spectra in accordance with it's racemate; e.e. 90%; $[\alpha]_D^{25}$ = + 49.3° (c, 0.70 in $CHCl_3$).

**General procedure for the immobilization of lipase AKG.**
Lipase AKG (500 mg) was dissolved in 10 ml of buffer. This was added to carrier material (2.0 g) (celite or hyflo super cell) which had been washed with water and buffer. After thoroughly mixing, the slurry was poured into a large petri-disk, and the water was evaporated overnight in the hood. The so obtained white powder was stored in the refrigerator and used for resolution experiments.

**Preparative resolution of diol 6.2e using immobilized lipase AKG**
In a representative experimental; diol **6.2e** (684 mg, 3.0 mmol) was dissolved in 10 ml of benzene and 3 ml of vinyl acetate. Lipase AKG (immobilized on celite at pH = 7.00, 1.25 g) was added and the mixture was stirred at room temperature in a sealed bottle. The conversion was monitored by TLC. After 70 h the reaction mixture was filtered and the residue was washed with ether. The filtrate was evaporated and the residue was purified by column chromatography (silica, ether/hexane 1:2) to give **6.2e** (339 mg, 1.49 mmol, 49%, e.e. 82% (as the monoacetate **6.6e** by chiral HPLC)) and **6.6e** (357 mg, 1.32 mmol, 44%, e.e. 94 % (chiral HPLC)); total yield 94%. From these data the conversion was determined as 0.468 and the enantiomeric ratio as 80.
The same experiment was repeated, but the reaction was now worked up after 93 h to give **6.2e** (228 mg, 1.26 mmol, 42%, e.e. >99% (as the monoacetate **6.6e** by chiral HPLC)) and **6.6e** (387 mg, 1.43 mmol, 48%, e.e. 83% (chiral HPLC); total yield 90%. From these data the conversion was determined as 0.546 and the enantiomeric ratio as 70.

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18. See appendix A at the end of this chapter for exact chromatographic data concerning the separation of each diol and acetate.

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33. At this moment we have, yet, not received any information from Amano concerning this problem. Prof. R.D. Schmid from the University of Stuttgart has, however, kindly provided us with some information concerning the isolation of a lipase from *Pseudomonas sp.* by Amano (Kojima, Y.; Yokoe, M.; Mase, T. *Biosci. Biotech. Biochem.* **1994**, *58*, 1564). This specific lipase (AK102) might be lipase AKG or lipase AK. At this moment the structure of this lipase from *Pseudomonas fluorescens* is not known. However, we think that lipase AKG is the same as lipase AK, only in its immobilized form on glass beads.

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# Appendix A

**Table 1. Resolution of diols 6.2 and corresponding acetates 6.6 by chiral HPLC on a Daicel OJ column**

| compound | eluent | flow (ml/min) | $R_{t1}$ (min) | $R_{t2}$ (min) | $\alpha$ |
|---|---|---|---|---|---|
| **6.2a** | hex/ipa 9:1 | 1.0 | 11.8 | 19.8 | 1.94 |
| **6.6a** | hex/ipa 9:1 | 1.0 | 13.3 | 33.3 | 3.00 |
| **6.2b** | hex/ipa 9:1 | 1.0 | 9.4 | 11.2 | 1.29 |
| **6.6b** | hex/ipa 9:1 | 1.0 | 12.7 | 19.7 | 1.74 |
| **6.2c** | hex/ipa 9:1 | 1.0 | 11.9 | 16.0 | 1.46 |
| **6.2c** | hex/ipa 9:1 | 0.5 | 23.3 (*S*) | 31.3 (*R*) | 1.41 |
| **6.6c** | hex/ipa 9:1 | 0.5 | 25.7 | 51.8 | 2.18 |
| **6.2d** | a) | | | | |
| **6.6d** | b) | | | | |
| **6.2e** | c) | | | | |
| **6.6e** | hex/ipa 9:1 | 1.0 | 21.5 (*S*) | 27.9 (*R*) | 1.34 |
| **6.2f** | hex/EtOH 95:5 | 1.0 | 27.9 (*R*) | 30.3 (*S*) | 1.10 |
| **6.6f** | hex/EtOH 95:5 | 1.0 | 21.2 | 25.3 | 1.22 |
| **6.2g** | hex/ipa 9:1 | 1.0 | 27.6 (*R*) | 41.0 (*S*) | 1.54 |
| **6.6g** | d) | | | | |
| **6.2h** | hex/ipa 9:1 | 1.0 | 31.9 | 41.1 | 1.32 |
| **6.6h** | d) | | | | |
| **6.2k** | hex/ipa 9:1 | 1.0 | 24.2 | 49.7 | 2.19 |
| **6.6k** | hex/ipa 9:1 | 1.0 | 28.4 | 34.4 | 1.23 |

a) Resolved on 50 m WCOT fused silica capillary GC column coated with CP cyclodextrin-B-2,3,6-M19 (Chrompack No. 7501) at 160°C; $R_t$ *E*-**6.2d** 37.8 and 38.3 min, *Z*-**6.2d** 43.3 and 43.7 min. b) Not resolved. c) Resolved as the corresponding acetate (via CAL acylation). d) Resolved as the corresponding diol (via LiOH/MeOH/$H_2O$ hydrolysis).

**Table 2. Resolution of diols 6.9, 6.11 and corresponding acetates by chiral HPLC on a Daicel OJ column**

| compound | eluent | flow (ml/min) | $R_{t1}$ (min) | $R_{t2}$ (min) | $\alpha$ |
|---|---|---|---|---|---|
| **6.9a** | hex/ipa 9:1 | 1.0 | 8.9 | 9.6 | 1.12 |
| **6.10a** | hex/ipa 9:1 | 1.0 | 10.9 | 13.6 | 1.35 |
| **6.9b** | hex/ipa 8:2 | 1.0 | 12.4 | 14.4 | 1.22 |
| **6.10b** | hex/ipa 8:2 | 1.0 | 15.9 | 18.8 | 1.23 |
| **6.9c** | hex/ipa 9:1 | 0.5 | 18.8 | 21.5 | 1.20 |
| **6.9c** | hex/EtOH 95:5 | 0.7 | 23.4 | 27.7 | 1.21 |
| **6.10c** | hex/ipa 9:1 | 1.0 | 11.5 | 15.7 | 1.47 |
| **6.10c** | hex/EtOH 95:5 | 0.7 | 20.9 | 41.6 | 2.16 |
| **6.9d** | hex/ipa 9:1 | 0.4 | 22.6 | 25.6 | 1.12 |
| **6.10d** | hex/ipa 9:1 | 0.4 | 29.7 | 36.5 | 1.31 |
| **6.11** | hex/ipa 9:1 | 0.5 | 20.3 | 23.2 | 1.20 |
| **6.12** | hex/ipa 9:1 | 1.0 | 11.2 | 13.4 | 1.26 |

# Chapter 7

# 5-Hydroxymethyl-[1,3]dioxolane-4-ones; enzymatic resolution and application in synthesis

## 7.1 Introduction

Functionalized chiral C3-synthons are among the most desired chiral building blocks in organic synthesis. Especially chiral glycerol derivatives are interesting as they can be used for the synthesis of several types of pharmacologically active compounds, of which the anti-hypertensive $\beta$-adrenergic blockers are probably the most important.[1] As glycerol (**7.1**) itself is not chiral (but prochiral), several derivatives of glycerol have been developed which are chiral (figure 7.1).

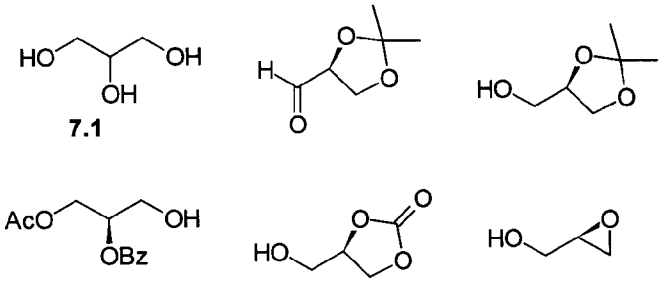
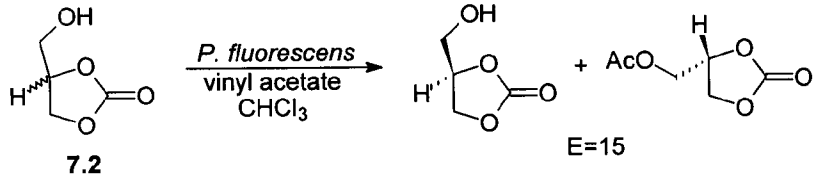



*Figure 7.1 Glycerol (7.1) and some of its chiral derivatives*

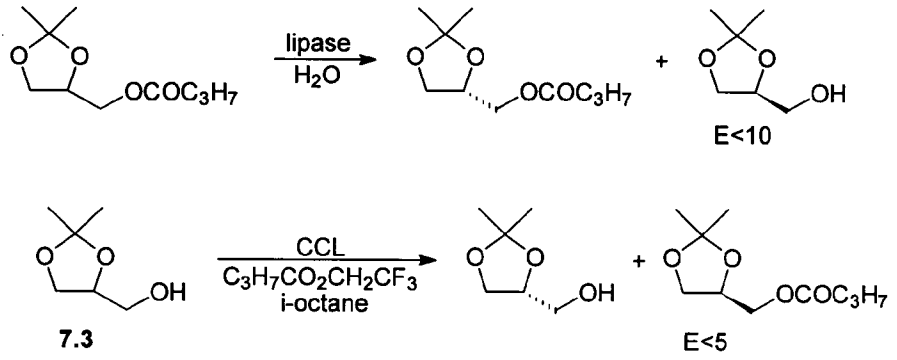
The chiral glycerol synthons can either be prepared by stereoselective synthesis from carbohydrates such as mannitol[2] or by enzymatic resolution procedures. These enzymatic procedures often consist of employing the 'meso-trick' (see chapter 5, scheme 5.5) on glycerol (or a direct derivative), but in such cases the optical purity of the product is seldom greater than 90%.[3] Of the racemic cyclic derivatives of glycerol, carbonate **7.2** has been resolved by enzymatic acylation




*Scheme 7.1 Lipase catalyzed resolution of glycerol carbonate*

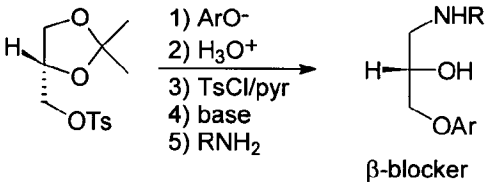
in the presence of a *Pseudomonas fluorescens* lipase. Although by this procedure nearly optically pure **7.2** was obtained, it is not completely satisfactory due to the moderate enantiomeric ratio of 15 (see chapter 5, section 5.4) (scheme 7.1).[4]

Also, attempts have been undertaken to resolve acetates of isopropylidene glycerol (solketal) **7.3** by enzymatic hydrolysis, but in these reactions enantiomeric ratios of $< 10$ were observed.[5] For the reverse process, enzymatic acylation of racemic isopropylidene glycerol, only moderate chiral discrimination was observed (scheme 7.2) as well.[6]




*Scheme 7.2 Lipase catalyzed resolution of isopropylidene glycerol*

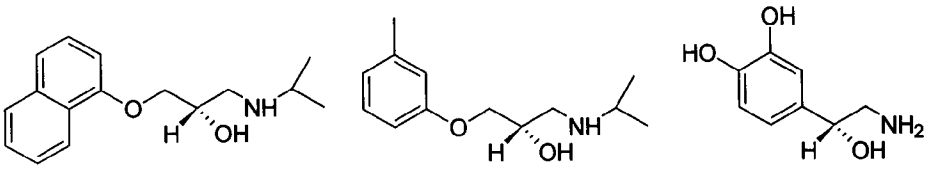
It has, however, been shown that chiral intermediates like **7.3** are easily converted to highly valuable β-blockers.[7] Usually such β-blockers are aryloxypropanolamines. Optically pure isopropylidene glycerol has been converted to its tosylate which was subsequently substituted by an aryloxide. After hydrolysis of the ketal and tosylation of the formed primary alcohol, conversion to an epoxide takes place. This epoxide is substituted with an amine to give the desired aryloxypropanolamine (scheme 7.3).




*Scheme 7.3 β-blocker synthesis from isopropylidene glycerol*

By changing the aryloxides and amines employed, one can successfully prepare several derivatives of this general structure.[7] β-Blockers show an

antihypertensive effect by blocking adrenergenic receptors. This effect is due to the strong resemblance of the (*S*) enantiomer to the adrenergenic hormone, (*R*)-noradrenaline. Some pharmacologically active β-blockers like propanolol and toliprolol are depicted in figure 7.2 together with noradrenaline.



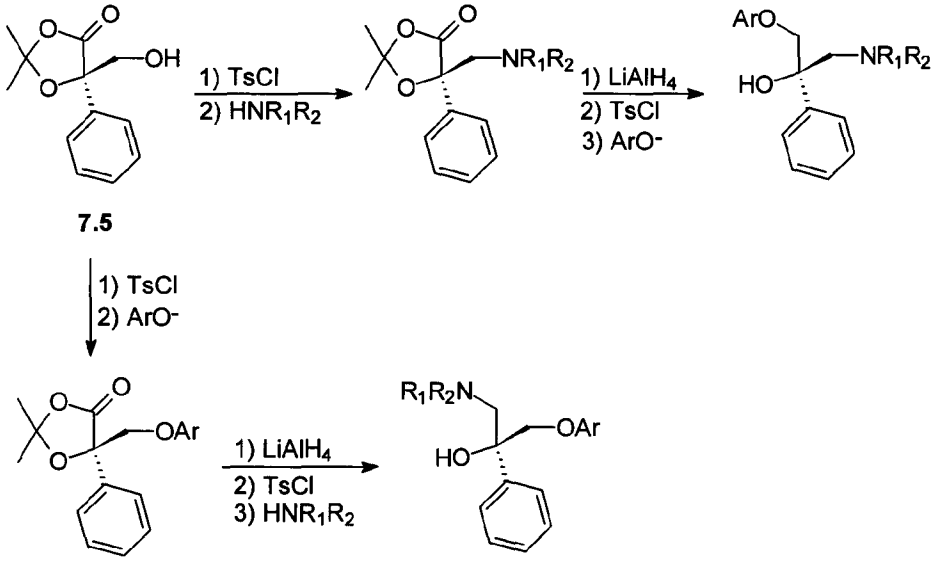

(*S*)-Propanolol (*S*)-Toliprolol (*R*)-Noradrenaline

*Figure 7.2 Some β-blockers and their analogy to noradrenaline*

Their common feature is that, besides the aryloxide and amine functionality, they contain a secondary hydroxyl group at the chiral center. Most β-blockers have a secondary amine group, substituted with an isopropyl residue. A large variety of aryloxy groups has been used in the development of new β-blockers.[8] The only position at which no substituent is introduced is on the chiral center itself; always a secondary hydroxyl group is present. It would therefore be interesting to prepare a glycerol analog having a tertiary chiral center. Such a compound might have new and interesting properties and give as well rise to the synthesis of a new class of aryloxypropanolamines having potential β-blocking properties. As we had experience with the synthesis of optically pure compounds having a tertiary chiral center, we wondered whether this built up experience could be applied to the synthesis of the valuable intermediates in optically active form.

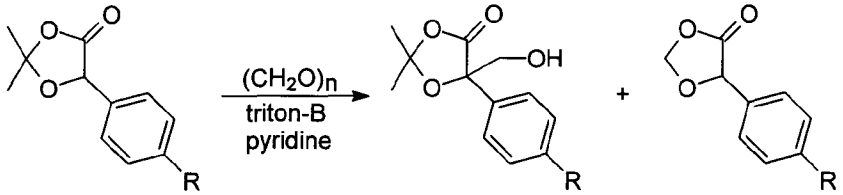
### 7.2 Preparation of hydroxymethyldioxolanones

The compound we envisioned to be a good target molecule was hydroxymethyldioxolanone **7.5**. In principle **7.5** might be accessible by hydroxymethylation of dioxolanone **7.4**, a compound we had previously successfully employed in the synthesis of tertiary mandelic acids and tertiary diols (see chapter 6). The target compound has the neccessary C3-skeleton of glycerol and the additional aryl substituent on the 2-position. Also, the three hydroxyl groups are masked as different functional groups (alcohol, cyclic ester, cyclic ketal) making the compound chiral. In principle, substition of the primary alcohol (as the tosylate) by an amine (or aryloxide) followed by reduction would give the 'half substituted' product. Another substitution by aryloxide (or amine) would then give rise to the desired β-blocker analog (scheme 7.4).
Using this strategy both enantiomers of the target compound could be prepared starting from a common (optically pure) intermediate depending on the chosen




*Scheme 7.4 Synthesis of both enantiomers of a tertiary aryloxypropanolamine from a common enantiomer of **7.5***

route. Intermediates like **7.5** have been described in literature only once as intermediate in the synthesis of triazole fungicides. Yields in this patent-reference are, however, not given.[9] Following this procedure (scheme 7.5) we indeed could produce **7.5** and analogs, but only in a low yield and not in a pure form.




**7.4** **7.5** **7.6**

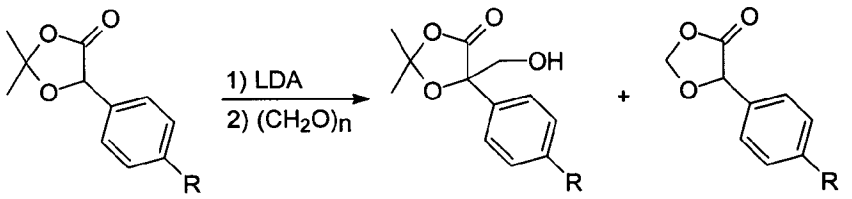
**a** R=H
**b** R=Br

*Scheme 7.5 Synthesis of hydroxymethyldioxolanones according to Ciba-Geigy*

A major byproduct, as determined by NMR, was the transacetalization of **7.4** with formaldehyde to yield **7.6**. In addition to **7.5** and **7.6** other minor products were formed as well. Overall, a complex reaction mixture was obtained from

which it was difficult to isolate the desired product in pure form. Only **7.5b** was isolated pure, due to its crystallinity.

A better procedure in our hands was the reaction between the lithium-enolate of **7.4a** and paraformaldehyde. Using this process a better yield (73% crude) of **7.5** was obtained, in a much cleaner reaction mixture. However, some **7.4a** was still transacetalized to formaldehyde ketal **7.6a** (scheme 7.6).

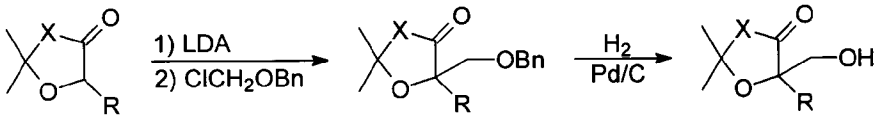



**7.4** **7.5** **7.6**

**a** R=H
**b** R=Br

*Scheme 7.6 Synthesis of hydroxymethyldioxolanones via the lithium enolate*

From these results it was clear that we had to turn to an alternative reagent and use an analog of formaldehyde which would give $\alpha$-alkylation, but no transacetalization. Such a reagent was found in benzyl chloromethyl ether. This alkyl halide can be prepared from formaldehyde, benzyl alcohol and hydrogen chloride[10] but is also available at a reasonable price from TCI. Previously it has been shown to be a powerful masked hydroxymethylating agent.[11] Alkylation of




**7.4** **7.7** **7.5**

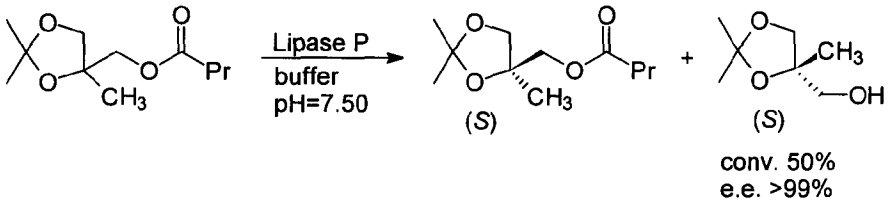
| | X | R | crude overall yield (%) |
|---|---|---|---|
| **a** | O | Ph | 91 |
| **c** | O | Me | 98 |
| **d** | NMe | Ph | 76 |

*Scheme 7.7 Synthesis of hydroxymethyldioxolanones 7.5 via alkylation followed by reductive debenzylation*

the enolate from **7.4** proceeded smoothly using benzyl chloromethyl ether and gave **7.7** in good yield. This compound can either be purified, or directly converted to **7.5** by reductive hydrogenation (scheme 7.7).
Via this approach several analogs of **7.5** have been prepared in good overall yields. Upon purification of the desired hydroxymethyldioxolanones one has to keep in mind that they may give retro-aldol reaction (liberation of formaldehyde) upon heating.[12]
We also tried to synthesize **7.5** directly from **7.4** and formaldehyde *via* an aldol-like condensation. For example, treatment of **7.4** in DMSO with paraformaldehyde in the presence of KOH yielded only starting material and also under acidic conditions (acetic acid/ acetic anhydride or $TiCl_4$) only starting material was recovered. We therefore concluded that the best way to prepare derivatives **7.5** is *via* the benzyl ether.

### 7.3 Enzymatic resolution of hydroxymethyldioxolanones in organic solvents

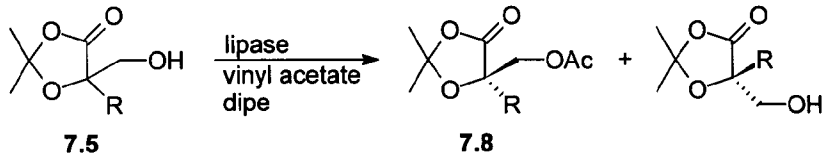
The primairy hydroxyl group in compounds **7.5** gave us a nice handle to perform lipase catalyzed resolution *via* enantioselective acylation. In the previous two chapters we have described several successful procedures to obtain alcohols in optically pure form this way. In section 7.1 we have, however, seen that results of resolution of glycerol derivatives using lipases usually are only moderate. A recent report by Wirz,[13] however, revealed that masked 2-methylglycerol derivatives could be resolved by lipases with very good chiral discrimination. For example, lipase P hydrolyzed the butyrate of isopropylidene-2-methylglycerol with absolute chiral discrimination (scheme 7.8).




*Scheme 7.8 Lipase catalyzed resolution of 2-methylglycerol derivatives*

Also several other lipases were shown to be very effective. In the reverse acylation process in organic solvents, extremely good chiral discriminations were observed as well. It is remarkable that introduction of a methyl group on the chiral center improved chiral recognition dramatically for this class of substrates. These results gave us enough confidence that it should be possible to resolve compounds **7.5** with high enantiodiscrimination by lipases as well.
Our first attempts were undertaken on **7.5a** which was most accessible as we had large quantities of the starting dioxolanone **7.4a** available for the synthesis of tertiary diols. Using diisopropyl ether (dipe) as solvent and vinyl acetate as

acyl donor **7.5a** was acylated in the presence of 6 lipases (scheme 7.9).




**7.5** **7.8**

*Scheme 7.9 Resolution of dioxolanones **7.5** by lipase catalyzed acylation*

Lipases AKG, PS, PPL and HPL gave, even after 17 days, no conversion. Of the two other lipases, *Candida cylindracae* (CCL) gave only moderate discrimination (E = 6), but *Candida antarctica* (CAL) was very efficient (E > 200).[14] Even at conversions approaching 50%, the produced acetate **7.8a** could only be detected as a single enantiomer (table 7.1). From a kinetic point of view the chiral discrimination must therefore be absolute, as it is the *product* which is obtained enantiomerically pure. It is also interesting to stress that *Candida cylindracae* shows an opposite chiral preference to this substrate as compared to *Candida antarctica*. Similar results were observed for **7.5b**. The preference of CCL was opposite to CAL and CCL showed moderate discrimination (E = 10); fortunately, CAL was efficient again, giving the product in 98% e.e. (E = 100).

**Table 7.1. Lipase catalyzed resolution of hydroxymethyldioxolanones 7.5a and b**

| substrate | lipase | time (h) | conv. (%) | e.e. alcohol (%) | e.e. acetate (%) | E |
|---|---|---|---|---|---|---|
| **7.5a** | CCL | 48 | 50 | 66 | 66 | 6 |
| **7.5a** | CAL | 96 | 32 | 46 | >99 | >200 |
| **7.5a** | CAL | 240 | 44 | 79 | >99 | >200 |
| **7.5b** | CCL | 20 | 50 | 80 | 60 | 10 |
| **7.5b** | CAL | 20 | 38 | 59 | 98 | 100 |

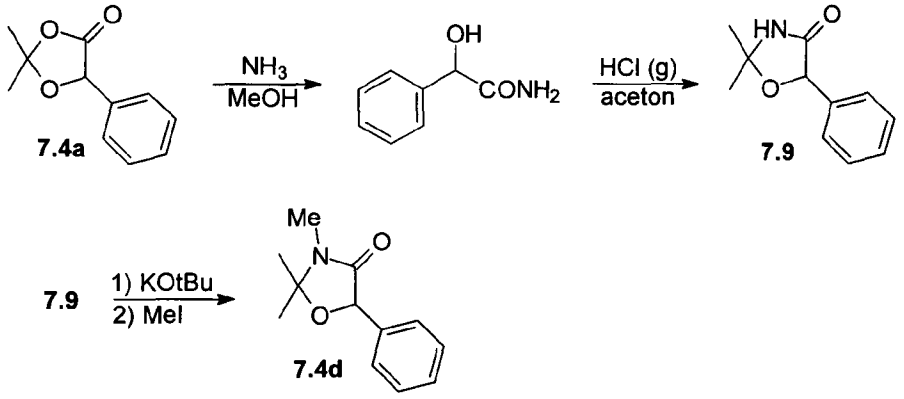
Another hydroxymethyldioxolanone, which is easily accesible, is **7.5c**. It is prepared straightforwardly from the dioxolanone of lactic acid. For this specific substrate not only CAL and CCL showed reactivity, but HPL and PPL as well. This is probably due to less steric repulsion for this substrate, making it more accesible for reaction. As observed more often, the substitution of an aromate for a methyl group increases reactivity, but decreases chiral discrimination significantly.[15] For example, in 20 h CAL converted **7.5c** to **7.8c** in 60% yield. In this way the remaining alcohol is enantiomerically pure, but the E-ratio is only 21. Also, CCL was more reactive and, as for **7.5a** and **b**, the other enantiomer

was obtained in enantiomerically pure form at 76% conversion (E = 7). HPL and PPL were less reactive, but especially PPL was more enantioselective. After 68 h, a conversion of 46% was achieved combined with an E of 40. The results for substrate **7.5c** are summarized in table 7.2.

**Table 7.2. Lipase catalyzed resolution of hydroxymethyldioxolanone 7.5c**

| lipase | time (h) | conv. (%) | e.e. alcohol (%) | e.e. acetate (%) | E |
|---|---|---|---|---|---|
| CAL | 20 | 60 | >98 | 64 | 21 |
| CCL | 20 | 76 | >98 | 31 | 7 |
| HPL | 68 | 31 | 38 | 86 | 17 |
| HPL | 184 | 47 | 72 | 82 | 20 |
| PPL | 20 | 29 | 38 | 91 | 40 |
| PPL | 68 | 46 | 76 | 89 | 40 |

A compound which might be interesting to resolve is hydroxymethyl oxazolidinone **7.5d**. Oxazolidinones like **7.5d** have already a built-in nitrogen functionality, making them easier to convert to the desired tertiary aryloxypropanolamines, as reduction of **7.5d** would give the amine.
Compound **7.5d** is prepared from the oxazolidinone **7.4d** as shown in scheme 7.7. Oxazolidinone **7.4d** was prepared from **7.4a**, following the synthesis outlined in scheme 7.10.



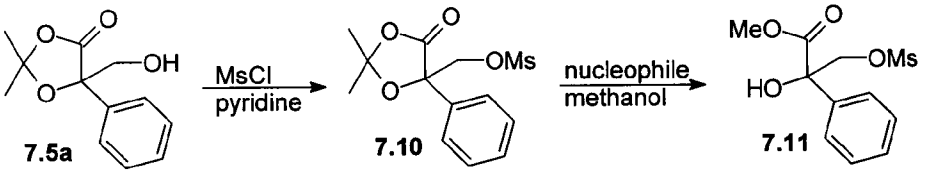

*Scheme 7.10 Synthesis of oxazolidinone **7.4d** from **7.4a***

Dioxolanones like **7.4a** are usually easilly converted into mandelamides.[16] In fact, probably the best method to prepare amides from *α*-hydroxy acids proceeds *via* such dioxolanones.[17] The primary mandelamide was subsequently

condensed with acetone to oxazolidinone **7.9** *via* a literature procedure.[18] This cyclic amide was alkylated by methyl iodide in the presence of potassium tert-butoxide under anhydrous conditions. Alkylation also takes place to a small extent at the α-position, but pure product **7.4d** was obtained after column chromatography. To shorten this procedure, we also tried to cyclize secondary mandelamides (such as N-methyl mandelamide, which would give **7.4d**) with acetone under identical conditions, but in all cases starting material was recovered and no condensation took place, although similar condensations have been reported in literature.[19] Also, the use of other mineral or Lewis acid catalysts did not lead to product formation.
Analogously to dioxolanones **7.5a** and **b**, **7.5d** was resolved smoothly by CAL. At approximately 54% conversion (72h) the remaining alcohol had an e.e. > 98%. The e.e. of the formed acetate was, however, difficult to determine due to the broad peak form of the second eluting enantiomer on HPLC. As this was the minor enantiomer, it was difficult to integrate, and therefore the conversion and E-value ($E \simeq 50$) (which are directly calculated from the e.e. of the product) could not be determined accurately. They were conservatively estimated and probably the real values are somewhat better. Resolution by CCL was for this specific substrate barely selective since E was only 1.2!

### 7.4 Derivatives of dioxolanone 7.5a

Tosylation and mesylation of hydroxymethyldioxolanone **7.5a** proceeds without problems according to scheme 7.11. However, upon trying to substitute the mesylate **7.10** with several nucleophiles (aryloxide, amine, azide) only starting material was recovered, even after prolongued reaction times (several days, reflux temperatures). The only other reaction that was detected was transesterification to give **7.11** if reactions were conducted in methanol (scheme 7.11).

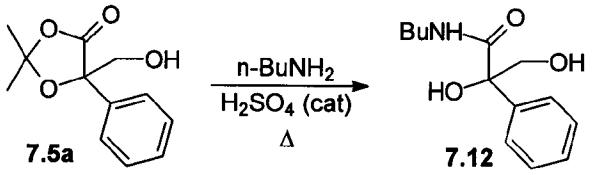



**7.5a** **7.10** **7.11**

*Scheme 7.11* *Attempted substitution of mesylate **7.10** resulting in ester formation*

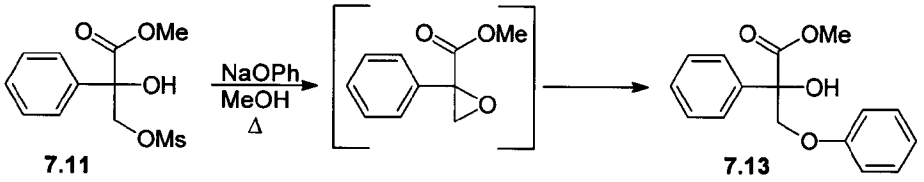
Therefore, we examined if **7.5a** could be directly converted to the amide in analogy to the synthesis of mandelamide from **7.4a** (scheme 7.10). By refluxing **7.5a** in acidic methanol in the presence of an amine only the methyl ester of phenylglycolic acid was produced. Upon omitting methanol as solvent, and

heating **7.5a** in pure amine no reaction took place. Upon adding a catalytic amount of $H_2SO_4$, however, **7.5a** was converted in n-butylamine to the amide **7.12** (scheme 7.12). This is the first step to the synthesis of a tertiary aryloxypropanolamine.



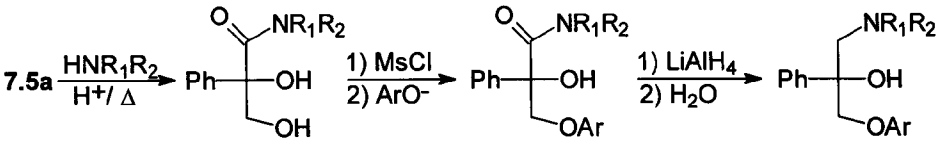

*Scheme 7.12 Conversion of **7.5a** to the amide by acidic catalysis*

Also, we converted mesylate **7.10** to methyl ester **7.11** by refluxing in acidic methanol. Whereas most of the compounds described in this chapter are sticky oils which are difficult to purify, compound **7.11** is a nice crystalline solid which can easily be purified. Substitution of **7.11** occurred neither with amines nor with sodium azide. Substitution did take place by the action of sodium salt of phenol in methanol. Under these conditions, probably first an epoxide is formed which subsequently ring opens to ether **7.13** (scheme 7.13). The yield of this reaction, only once performed, was somewhat disappointing (30% yield) but might be improved in the future.




*Scheme 7.13 Substitution of mesylate **7.13** by sodium aryloxide*

We were running out of time at this moment and no further attempts were undertaken to finish the total synthesis of a tertiary β-blocker analog. However, to arrive at the total synthesis of a potential β-blocker from **7.5a** of combination of the reactions of schemes 7.12 and 7.13 could be the basis. First **7.5a** would have to be amidated analogously to scheme 7.12. Subsequent mesylation of the primary hydroxyl group followed by substitution (*via* intermediate epoxide) by an aryloxide would give the precursor for such a β-blocker. In a final step reduction of the amide would give the desired amine (scheme 7.14). Although this is still 'paper-work', initial experiments have shown that such a series of transformations starting from **7.5a** is possible.




*Scheme 7.14 Synthesis of a tertiary β-blocker from* ***7.5a***

## 7.5 Conclusions and outlook

In this chapter we have shown that hydroxymethyl-[1,3]dioxolane-4-ones are easily accessible from α-hydroxy acids like mandelic and lactic acid via the acetonide. Direct hydroxymethylation of these derivatives was shown to be possible, but both yields and purity of the crude products are disappointing. A better procedure was found in the use of benzyl chloromethyl ether as a masked hydroxymethylating agent. Also we have shown that hydroxymethyldioxolanones **7.5** are good substrates for lipase catalyzed resolutions. For all four compounds **7.5** prepared it was possible to obtain enantiomerically pure material using either CAL or PPL as biocatalyst. In some cases chiral recognitions were absolute as only one enantiomer was converted! So far reactions have been run on an analytical scale only, but since both CAL en PPL are cheap and readily available lipases reactions should be easy to scale up. Using racemic **7.5a** we have shown that it is possible to build in both the amine and aryloxy functionality. Combination of these two procedures could in principle give rise to the preparation of the desired tertiary analogs of the pharmaceuticaly active aryloxypropanolamines.

## 7.6 Experimental

### General

For general remarks see chapter 2. For the suppliers of lipases see table 6.1. Benzyl chloromethyl ether (90%) was purchased from TCI.

### 1,5,5-Trimethyl-3-phenyloxazolidine-2-one (7.4d)

Under an atmosphere of nitrogen using dry glassware, oxazolidinone **7.9**[18] (1.91 g, 10 mmol) was dissolved in 20 ml of dry THF. After cooling to -20 °C, KOtBu (1.12 g, 10 mmol) was added. The mixture was stirred for 5 min and methyl iodide (2.13 g, 0.93 ml, 15 mmol) was added. The mixture was stirred for 3h and quenched with $NH_4Cl$ solution. The reaction mixture was extracted three times with EtOAc and the combined organic layers were washed with brine. After drying ($Na_2SO_4$) and evaporation a yellow oil (1.97 g, 9.6 mmol, 96%) was obtained which was purified by column chromatography (silica,

$CH_2Cl_2$) to provide the pure title compound (1.50 g, 7.3 mmol, 73%); $^1$H-NMR ($CDCl_3$); $\delta$ 1.49 (s, 3H), 1.57 (s, 3H), 2.84 (s, 3H), 5.26 (s, 1H), 7.24-7.48 (m, 5H); $^{13}$C-NMR ($CDCl_3$); $\delta$ 25.2 (q), 25.5 (q), 26.9 (q), 78.1 (d), 93.9 (s), 126.5 (d), 128.3 (d), 128.5 (d), 137.0 (s), 169.4 (s).

**2,2-Dimethyl-5-hydroxymethyl-5-phenyl-[1,3]dioxolane-4-one (7.5a) using paraformaldehyde**

In an atmosphere of nitrogen using dry glassware, diisopropylamine (3.5 ml, 25 mmol) was dissolved in 50 ml of dry THF. After cooling to -80 °C n-Buli (14 ml, 1.6N in hexane, 22 mmol) was added. After stirring for 15 min the mixture was recooled to -80 °C and a solution of dioxolanone **7.4a** (3.84 g, 20 mmol) in dry THF was added dropwise. The mixture was stirred for 15 min, and again recooled to -80 °C. Paraformaldehyde (750 mg, 25 mmol) was added, and the mixture was slowly allowed to reach room temperature and stirred overnight. Saturated $NH_4Cl$ solution (50 ml) was added and the reaction mixture was extracted twice with ether. The combined organic layers were washed with brine and dried ($Na_2SO_4$) and evaporated to give crude **7.5a** (3.22 g, 14.5 mmol, 73%). This material was distilled (125 °C/0.02 mm Hg) to give a nearly pure yellow oil (1.97g, 8.87 mmol, 44%). For physical data see below.

**2,2-Dimethyl-5-hydroxymethyl-5-phenyl-[1,3]dioxolane-4-one (7.5a) via the benzyl ether 7.7a**

In an atmosphere of nitrogen using dry glassware, diisopropylamine (10.5 ml, 75 mmol) was dissolved in 100 ml of dry THF. After cooling to -80 °C Buli (27 ml, 2.5N in hexane, 67 mmol) was added. After stirring for 15 min the mixture was recooled to -80 °C and a solution of dioxolanone **7.4a** (11.5 g, 60 mmol) in dry THF was added dropwise. The mixture was stirred for 15 min and again recooled to -80 °C. Benzyl chloromethyl ether (90%) (10.4 ml, 65 mmol) in dry THF was added dropwise and the mixture was allowed to reach room temperature (3h) and stirred overnight. Saturated $NH_4Cl$ solution (100 ml) was added and the reaction mixture was extracted three times with ether. The combined organic layers were washed with brine and dried ($Na_2SO_4$) and evaporated to give crude **7.7a** (19.85 g) containing a small amount benzyl alcohol. Part of this crude material was purified by column chromatography (silica ether/hexane 1:25) to provide pure **7.7a**; $^1$H-NMR ($CDCl_3$); $\delta$ 1.53 (s, 3H), 1.78 (s, 3H), 3.62 (d, $J_{AB}$ = 11 Hz, 1H), 3.92 (d, $J_{AB}$ = 11 Hz, 1H), 4.67 (s, 2H), 7.27-7.45 (m, 8H), 7.69-7.75 (m, 2H); $^{13}$C-NMR ($CDCl_3$); $\delta$ 27.44 (q), 28.18 (q), 73.65 (t), 75.14 (t), 84.10 (s), 110.58 (s), 125.20 (d), 127.50 (d), 127.66 (d), 128.36 (d), 128.45 (d), 128.52 (d), 136.18 (s), 137.50 (s); HRMS m/z calcd 312.136. Found 312.136. The rest of the crude material (13.23 g, 42 mmol) was dissolved in 50 ml of EtOH and 200 mg 5% Pd on carbon was added. The mixture was hydrogenated at 40 psi during 48h in a Parr apparatus, after which it was filtered and evaporated to give crude **7.5a** (8.55 g, 38.5 mmol, 91%) as an oil. Pure material was obtained by bulb-to-bulb-distillation

(145 °C/ 0.25 mm Hg) to give the title compound **7.5a** as a colourless oil (7.35 g, 33 mmol, 78%). An analytically pure sample was obtained by column chromatography (silica, ether/hexane 1:2); $^1$H-NMR ($CDCl_3$); $\delta$ 1.47 (s, 3H), 1.76 (s, 3H), 2.47 (dd, $J$ = 4.4 and 8.3 Hz, 1H), 3.67 (dd, $J_{AB}$ = 11 HZ, $J_{OH}$ = 4.4 Hz, 1H), 4.01 (dd, $J_{AB}$ = 11 HZ, $J_{OH}$ = 8.3 Hz, 1H), 7.25-7.36 (m, 3H), 7.62-7.66 (m, 2H); $^{13}$C-NMR ($CDCl_3$); $\delta$ 27.56 (q), 27.91 (q), 68.13 (t), 85.23 (s), 110.91 (s), 125.06 (d), 128.56 (d), 136.11 (s); HRMS m/z (-$CH_2O$) calcd 192.079. Found 192.079; Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.47; H, 6.32.

**2,2-Dimethyl-5-hydroxymethyl-5-(4-bromophenyl)-[1,3]dioxolane-4-one (7.5b) according to Ciba-Geigy**[9]

Dioxolanone **7.4b**[20] (5.42 g, 20 mmol) was dissolved in 35 ml of pyridine, Paraformaldehyde (2.4 g, 80 mmol) and triton-B (2 ml, 40% in MeOH) were added. The mixture was stirred overnight and cooled to -5 °C. Acetic acid was added until the pH reached 6.5-7.0 and the mixture was poured onto ice-water. The slurry was extracted three times with $CH_2Cl_2$ and the combined organic layers were dried on $Na_2SO_4$. The organic fraction was evaporated at a rotary evaporator and subsequently most pyridine was evaporated at low pressure (0.01 mm) at 50 °C. The remaining oil was dissolved in ether and stored overnight at 4 °C to give **7.5b** as white needles (1.33 g, 4.42 mmol, 22%); mp 131-132 °C (lit.,[9] 123-127 °C); $^1$H-NMR ($CDCl_3$); $\delta$ 1.47 (s, 3H), 1.75 (s, 3H), 2.05 (br, 1H), 3.65 (d, $J_{AB}$ = 12 Hz, 1H), 3.97 (d, $J_{AB}$ = 12 Hz, 1H), 7.54 (s, 4H); $^{13}$C-NMR ($CDCl_3$); 27.54 (q), 27.97 (q), 68.00 (t), 84.60 (s), 110.81 (s), 123.03 (s), 126.87 (d), 131.77 (d), 135.06 (s).

**2,2,5-Trimethyl-5-hydroxymethyl-[1,3]dioxolane-4-one (7.5c)**

Dioxolanone **7.4c**[15] (2.60 g, 20 mmol) was alkylated with benzyl chloromethyl ether (3.46 ml) analogously to the procedure described above for **7.4a** to give **7.7c** (5.85g, 100%) contaminated with benzyl alcohol. A part of this material was purified by column chromatography (silica, EtOAc/hexane 1:9) to give a colourless oil which solidified upon standing; mp 48-51 °C; $^1$H-NMR ($CDCl_3$); $\delta$ 1.34 (s, 3H), 1.53 (s, 3H), 1.57 (s, 3H), 3.45 (d, $J_{AB}$ = 10 Hz, 1H), 3.57 (d, $J_{AB}$ = 10 Hz, 1H), 7.26 (s, 5H); $^{13}$C-NMR ($CDCl_3$); $\delta$ 21.55 (q), 27.51 (q), 28.99 (q), 73.40 (t), 80.82 (s), 110.18 (s), 127.50 (d), 127.66 (d), 128.36 (d), 137.64 (s), 173.91 (s); HRMS m/z calcd 250.120. Found 250.120; Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.09; H, 7.23. The rest of the crude **7.7c** (1.90 g, 7.6 mmol) was dissolved in EtOH and hydrogenated in a parr apparatus with a catalytic amount of Pd/C (5%) in 48h. After filtration crude **7.5c** was obtained (1.19 g, 7.44 mmol, 98%) of which a part was purified by column chromatography (silica, EtOAc/hexane 1:9) to give the pure title compound; $^1$H-NMR ($CDCl_3$); $\delta$ 1.35 (s, 3H), 1.56 (s, 3H), 1.58 (s, 3H), 2.93 (br dd, $J$ = 7.4 Hz and 4.7 Hz, 1H), 3.50 (dd, $J_{AB}$ = 12 Hz, $J$ = 4.7 Hz,

1H), 3.68 (dd, $J_{AB}$ = 12 Hz, $J$ = 7.4 Hz, 1H); $^{13}$C-NMR ($CDCl_3$); $\delta$ 20.92 (q), 27.66 (q), 28.73 (q), 66.09 (t), 81.74 (s), 110.81 (s), 174.17 (s); HRMS m/z calcd (- $CH_3$) 145.050. Found 145.050.

**1,5,5-Trimethyl-3-hydroxymethyl-3-phenyloxazolidine-2-one (7.5d)**
Using a procedure analogous to **7.5a** and **7.5c**, oxazolidinone **7.4d** (1.47 g, 7.2 mmol) was alkylated with benzyl chloromethyl ether (1.26 ml). The quantitatively obtained **7.7d** (contaminated with benzyl alcohol) was dissolved in EtOH and hydrogenated in a parr apparatus (72 h) using a catalytic amount of Pd/C (5%). After filtration and evaporation there remained crude **7.5d** (1.28 g, 5.4 mmol, 76%). This was purified by column chromatography (silica, gradient ether/hexane 1:1 to pure ether) to provide the title compound (0.50 g, 2.13 mmol, 30%) as an oil which solidified upon standing. The reason for this low yield is unclear; mp 87.0-89.3°C; $^1$H-NMR ($CDCl_3$); $\delta$ 1.39 (s, 3H), 1.82 (s, 3H), 2.60 (br, 1H), 2.83 (s, 3H), 3.60 (dd, $J$ = 12 Hz and $J$ = 4.6 Hz, 1H), 4.02 (dd, $J$ = 12 Hz and $J$ = 8.1 Hz, 1H), 7.27-7.37 (m, 3H), 7.68-7.73 (m, 2H); $^{13}$C-NMR ($CDCl_3$); $\delta$ 25.62 (q), 26.61 (q), 26.90 (q), 67.89 (t), 85.92 (s), 93.70 (s), 125.55 (d), 127.89 (d), 128.15 (d), 138.70 (s); HRMS m/z calcd (- $CH_2O$) 205.109. Found 205.110; Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.52; H, 7.27; N, 5.98.

**General procedure for the lipase catalyzed resolution of 7.5**
Hydroxymethyldioxolanone **7.5** (0.3 mmol) was dissolved in 1 ml of diisopropylether and 0.2 ml of vinyl acetate. Lipase (20 mg) was added and the mixture was stirred at room temperature. At regular intervals a 0.1 ml sample was taken which was filtered over celite in a pasteur pipette. The celite was washed with 1 ml of $CH_2Cl_2$ and the filtrate was evaporated to dryness. The residue was dissolved in 1 ml of i-propanol and analyzed as indicated.
**7.5a**: The crude mixture was directly analyzed by chiral HPLC using a Daicel OJ column. As mobile phase 20% ipa in hexane was used at a flow rate of 1 ml/min. Retention times for **7.5a**; 7.5 and 10.6 min; for the acetate **7.8a**; 12.4 and 14.9 min.
**7.5b**: The crude mixture was directly analyzed by chiral HPLC using a Daicel OJ column. As mobile phase 20% ipa in hexane was used at a flow rate of 0.5 ml/min. Retention times for **7.5b**; 13.8 and 45.2 min; for the acetate **7.8b**; 20.7 and 23.6 min.
**7.5c**: The crude filtrate was directly analyzed by chiral GC using a FS-LIPODEX C column at an oven temperature of 125°C; retention times **7.5c**; 164.8 and 172.2 min; for the acetate **7.8c**; 145.6 and 147.3 min.
**7.5d**: The alcohol and acetate were separated by column chromatography (silica, ether) and individually analyzed by chiral HPLC using a Daicel OJ column. For **7.5d** 10% ipa in hexane was used as mobil phase at a flow rate of 0.5 ml/min, for **7.8d** 20% ipa in hexane at a flow rate of 1.0 ml/min. Retetention times for **7.5d**; 19.5 and 23.3 min; for the acetate **7.8d**; 7.1 and 16.4 min.

**Methanesulfonic acid 2,2-dimethyl-5-oxo-4-phenyl-[1,3]dioxolan-4-ylmethyl ester (7.10)**

Hydroxymethyldioxolanone **7.5a** (2.22 g, 10 mmol) was dissolved in 20 ml of pyridine. The solution was cooled in an ice-salt bath and mesylchloride (0.85 ml, 11 mmol) was added as an etheral solution. The mixture was stirred for 1h at 0°C and subsequently 1 h at room temperature. The mixture was poured on ice water and EtOAc was added. The mixture was washed three times with aqeouos HCL (1M) and brine. After drying ($Na_2SO_4$) the mixture was evaporated to dryness. Last traces of pyridine were removed in a kugelrohr apparatus at 50°C/ 0.02 mm Hg to give a near quantitative yield of **7.10** which was used without further purification; $^1$H-NMR ($CDCl_3$); $\delta$ 1.47 (s, 3H), 1.76 (s, 3H), 3.03 (s, 3H), 4.30 (d, $J_{AB}$ = 9 Hz, 1H), 4.47 (d, $J_{AB}$ = 9 Hz, 1H), 7.28-7.49 (m, 3H), 7.63-7.73 (m, 2H).

**2-Hydroxy-3-methanesulfonyloxy-2-phenylpropionic acid methyl ester (7.11)**

Mesylate **7.10** (1.92 g, 6.41 mmol) was dissolved in 20 ml of MeOH. A catalytic amount of sulfuric acid was added and the mixture was refluxed for four days. It was poured on water and extracted three times with ether. The combined organic layers were washed with brine and dried ($Na_2SO_4$). After evaporation there remained an oil which crystallized upon standing. It was recrystallized from EtOAc/hexane to give pure **7.11** (1.23 g, 4.49 mmol, 70%); mp 94.0-95.0°C; $^1$H NMR ($CDCl_3$); $\delta$ 3.08 (s, 3H), 3.89 (s, 3H), 4.0 (br, 1H), 4.41 (d, $J_{AB}$ = 10.7 Hz, 1H), 4.83 (d, $J_{AB}$ = 10.7 Hz, 1H), 7.37-7.44 (m, 3H), 7.59-7.64 (m, 2H); $^{13}$C NMR ($CDCl_3$); $\delta$ 37.83 (q), 53.89 (q), 73.56 (t), 125.50 (d), 128.74 (d), 129.05 (d), 136.18 (s); HRMS calcd m/z 274.051. Found 274.051; Anal. Calcd for $C_{11}H_{14}SO_6$: C, 48.17; H, 5.14. Found: C, 48.23; H, 5.15.

***N*-Butyl-2,3-dihydroxy-2-phenylpropionamide (7.12)**

Dioxolanone **7.5a** (480 mg, 2.16 mmol) was refluxed for 48 h in n-butylamine (25 ml) in the presence of a catalytic amount of sulfuric acid. The solution was evaporated to dryness to give the title compound as a yellow oil based on NMR. Yet, no attempts were undertaken to purify this compound; $^1$H NMR ($CDCl_3$); $\delta$ 0.90 (t, $J$ = 7 Hz, 3H), 1.17-1.52 (m, 4H), 3.13-3.26 (m, 2H), 3.62 (d, $J_{AB}$ = 10 Hz, 1H), 4.35 (d and br, 3H), 7.06 (br, 1H), 7.22-7.44 (m, 3H), 7.56-7.68 (m, 2H).

**2-Hydroxy-3-phenoxy-2-phenylpropionic acid methyl ester (7.13)**

Mesylate **7.11** (507 mg, 1.85 mmol), phenol (1.88 g, 20 mmol) and NaOMe (1.08 g, 20 mmol) were dissolved in 20 ml MeOH. The mixture was refluxed overnight. The mixture was poured on water and extracted three times with EtOAc. The organic layers were washed three times with 2N aqeouos KOH and brine. After drying ($Na_2SO_4$) the mixture was evaporated to give crude **7.13**

(151 mg, 0.56 mmol, 30%) as an oil which was not further purified, yet; $^1$H NMR ($CDCl_3$); $\delta$ 3.84 (s, 3H), 4.20 (d, $J_{AB}$ = 9.3 Hz, 1H), 4.70 (d, $J_{AB}$ = 9.3 Hz, 1H), 6.82-7.04 (m, 3H), 7.20-7.44 (m, 5H), 7.63-7.76 (m, 2H); $^{13}$C NMR ($CDCl_3$); $\delta$ 53.42 (q), 73.78 (t), 114.97 (d), 121.51 (d), 125.69 (d), 128.56 (d), 129.49 (d), 137.50 (s), 158.26 (s).

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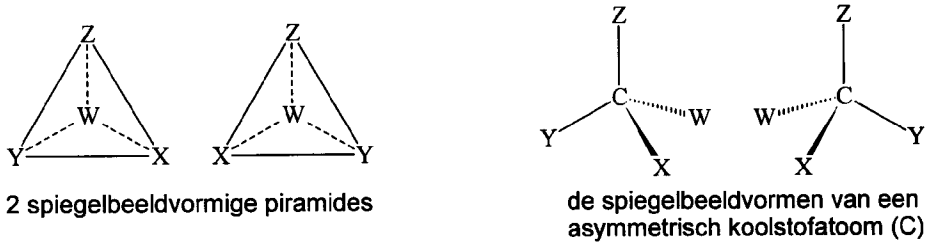
# Samenvatting

### *Algemene achtergrond*

In dit proefschrift wordt de synthese van nieuwe chirale verbindingen beschreven. Het verschijnsel chiraliteit is één van de meest intrigerende onderwerpen in de organische chemie. Chiraliteit is niet beperkt tot chemie alleen, maar kan gevonden worden in al het dagelijks leven. Chiraliteit heeft te maken met de vorm van een bepaald object. Wanneer een object niet tot dekking te brengen valt met zijn spiegelbeeldvorm (gesuperpositioneerd) noemen we zo'n object *chiraal*. Bekende chirale objecten in het dagelijks leven zijn bijvoorbeeld onze handen. Ze lijken identiek, maar wanneer je ze exact op elkaar probeert te plaatsen dan lukt dat niet. Ze hebben echter wel een bepaalde relatie, en dat is dat ze spiegelbeelden zijn. Hetzelfde geldt voor bepaalde moleculen. Ze lijken hetzelfde, maar eigenlijk zijn ze spiegelbeelden, en dus *niet* identiek. Deze beide spiegelbeeldvormen noemen we de *enantiomeren*. De oorzaak van de spiegelbeeldisomerie is vaak de aanwezigheid van een *asymmetrisch* koolstofatoom (C) in het molecule. Door de ruimtelijke positionering van vier verschillende groepen (W, X, Y en Z) op zo'n koolstofatoom ontstaat een soort van piramide (een *tetraëder*) die in twee spiegelbeeldvormen voorkomt (figuur 1).




2 spiegelbeeldvormige piramides

de spiegelbeeldvormen van een asymmetrisch koolstofatoom (C)

*Figuur 1*

Een verschijnsel dat gerelateerd is aan chiraliteit is *optische rotatie*. Voor het merendeel van chirale verbindingen geldt dat de enantiomeren in staat zijn om het vlak van gepolariseerd licht te draaien (dit is het type licht zoals een polaroid-bril het doorlaat). Het ene enantiomeer laat het licht linksom roteren, het andere laat het licht rechtsom roteren. Een voorbeeld van zo'n chirale verbinding is melkzuur. De enantiomeren van melkzuur kunnen gepolariseerd licht dus rechts- of linksom roteren. Beide vormen worden in de natuur geproduceerd (door bacteriën) en kunnen, onder andere, gevonden worden in yoghurt en biogarde (links- of rechtsdraaiend melkzuur). Een ander fenomeen van chirale verbindingen is dat ze doorgaans een verschillende interactie aangaan met andere chirale verbindingen. Dit kun je vergelijken met de interactie van een hand (een chiraal object) met een linker- of rechter handschoen (dit zijn ook

chirale objecten). De hand zal slechts goed in één van de beide handschoenen passen. Aangezien een groot gedeelte van belangrijke moleculen in de natuur chiraal zijn (zoals DNA, eiwitten, hormonen en suikers), hebben de enantiomeren van een chirale verbinding vaak een verschillende uitwerking in de natuur. De interactie van het ene enantiomeer met een bepaald chiraal molecule in ons lichaam is vaak groter dan die van het andere enantiomeer. Soms is het gevolg een klein verschil in activiteit (uitwerking), maar er zijn legio gevallen bekend waarin één van de enantiomeren het gewenste effect veroorzaakt (bijvoorbeeld als medicijn), terwijl het andere enantiomeer buitengewoon giftig blijkt te zijn. Aangezien een groot gedeelte van de heden ten dage gebruikte medicijnen, voedingsadditieven en gewasbeschermingsmiddelen bestaat uit chirale verbindingen is het van belang om routes te vinden tot enantiomeer zuivere verbindingen. Het lijkt triviaal om op moleculair niveau selectief één spiegelbeeldvorm te produceren, maar in de praktijk blijkt dit een lastig probleem te zijn. Zoals misschien is voor te stellen heb je een bepaalde chirale moleculaire 'mal' nodig om nieuwe chirale producten te maken. Een klassieke organische synthese (zonder chirale hulpstof) levert echter altijd een 1:1 mengsel van de enantiomeren op (een *racemaat*). Deze dienen na afloop gescheiden te worden, en het ongewenste enantiomeer kan als afval beschouwd worden. Vanuit een milieu- en economisch oogpunt is een synthese die bij voorkeur één van de enantiomeren oplevert dus van belang. Er zijn een aantal manieren om dit te doen, en de drie methodes die beschreven worden in dit proefschrift zal ik kort uitleggen.

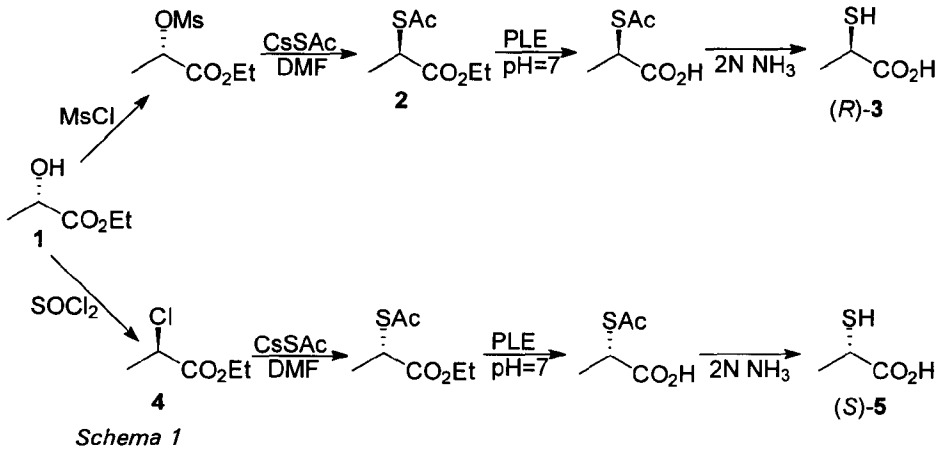
a) Allereerst kun je gebruik maken van een uitgangsstof die al bestaat uit slechts één spiegelbeeldvorm. Zo'n enantiomeer zuivere verbinding kan vaak gevonden worden in de natuur. Vervolgens kun je er een aantal omzettingen mee doen om zodoende het gewenste optisch actieve product te maken (dit noemen we *asymmetrische synthese*). Bekende voorbeelden van natuurlijk voorkomende chirale verbindingen zijn aminozuren, kinine, melkzuur en suiker.
b) Je kunt ook gebruik maken van een optisch zuivere verbinding als *katalysator* tijdens een synthese stap. Het begrip katalyse houdt in dat je een klein beetje stof toevoegd tijdens een reactie, en dat je deze stof aan het eind van de reactie onveranderd terug wint (het raakt dus niet op). Het belangrijkste effect van de katalysator is dat hij er voor zorgt dat de reactie sneller verloopt. Dit gebeurt door de stoffen op een bepaalde manier met elkaar te laten reageren zodat minder energie nodig is. Wanneer deze katalysator nu chiraal is, werkt hij als een soort chirale mal, en levert dan ook chiraal product op. Dit proces is aantrekkelijk aangezien een kleine hoeveelheid enantiomeer zuiver materiaal (de katalysator) grote hoeveelheden nieuw enantiomeer verrijkt materiaal kan produceren. Dit type aanpak noemen we *katalytische asymmetrische synthese*.
De katalysatoren die in deze reacties gebruikt worden kunnen zowel synthetisch als natuurlijk van aard zijn.
c) Ook de natuur werkt met zijn eigen katalysatoren. Deze katalysatoren worden

*enzymen* genoemd en zijn opgebouwd uit chirale aminozuren. Tegenwoordig zijn we in staat om deze enzymen te winnen uit bijvoorbeeld planten, schimmels, gisten en slachtafval. Een bekend soort enzymen zijn de *lipases*. In de natuur zorgen deze lipases er voor dat vetten (*lipiden*) omgezet worden in vetzuren en glycerol. Dit doen ze door een bepaald type chemische binding, een *ester*, te *hydrolyseren* (te splitsen). Hier wordt dankbaar gebruik van gemaakt door wasmiddelfabrikanten. Door lipases toe te voegen aan wasmiddelen worden op een milieuvriendelijke wijze (vet)vlekken verwijderd. Voor de hydrolyse van een ester binding heeft een lipase echter water nodig. Door nu te gaan werken in een oplosmiddel dat geen water bevat (een *organisch* oplosmiddel) kunnen enzymen echter ook ester bindingen maken! Dit is iets waar we gebruik van maken in de organische chemie. Het aardige is dat lipases slechts in één enantiomere vorm voorkomen. Bij het toedienen van een racemisch alcohol (een 1:1 mengsel van enantiomeren) aan het enantiomeer zuivere lipase zal bij voorkeur één van de enantiomeren omgezet worden in het ester; het andere reageert langzamer. Na een bepaald tijdstip zal van het alcohol één van beide enantiomeren totaal opgegeten zijn (omgezet in het ester) en is het achterblijvende alcohol dus enantiomeer zuiver. Dit materiaal kan dan in enantiomeer zuivere vorm geïsoleerd worden. Soms is het zelfs zo dat exclusief één enantiomeer omgezet wordt, terwijl het andere enantiomeer totaal ongemoeid blijft.

Er bestaan vele soorten chirale verbindingen en honderden onderzoeksgroepen zijn werkzaam op het gebied van chiraliteit. Als wetenschapper moet je dus je grenzen afbakenen en je op een bepaald doel richten. Twee research gebieden in onze onderzoeksgroep zijn het maken van chirale zwavel bevattende verbindingen, zogenaamde thiolen, en de synthese van verbindingen met een tertiair chiraal koolstofatoom (op het chirale centrum zitten, behalve 1 functionele groep, 3 verschillende koolstofstaarten). Aan beide klassen van verbindingen is wereldwijd niet zo veel onderzoek gedaan. Bovendien kunnen deze verbindingen interessante toepassingen hebben als chirale katalysator of als bouwsteen voor farmacologisch actieve verbindingen. Daarom besloten we ons te richten op de synthese van deze types van verbindingen in optisch zuivere vorm en tevens te kijken naar hun mogelijke toepassingen.
Na deze algemene inleiding over de achtergrond van mijn onderzoek zal ik nu een meer chemische samenvatting geven van de inhoud van het proefschrift.

***Inhoud van het proefschrift***

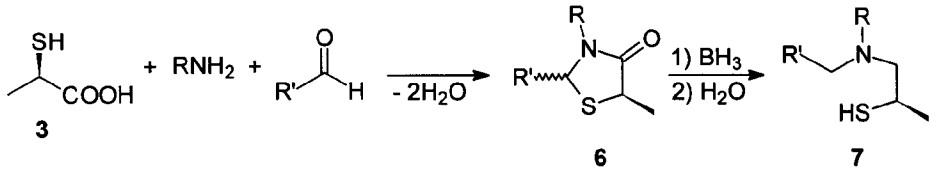
Een algemene introduktie over het werk beschreven in dit proefschrift wordt gegeven in hoofdstuk 1. In hoofdstuk 2 wordt een nieuwe synthese beschreven van de beide enantiomeren van thiomelkzuur. Thiomelkzuur is een analoog van het natuurlijk voorkomende melkzuur, waarbij de hydroxy groep vervangen is door een thiol groep. In het verleden is het (*R*)-enantiomeer van deze verbinding geprepareerd in onze groep, maar de gevolgde route is omslachtig. Aangezien optisch zuiver thiomelkzuur de laatste jaren gebruikt is voor de synthese van nieuwe medicijnen (o.a. tegen maagzweren) en is ingebouwd in peptides, was het voor ons interessant om te onderzoeken of we een verbeterde procedure voor (*R*)-thiomelkzuur konden vinden. Tevens besloten we te onderzoeken of we ook (*S*)-thiomelkzuur op een eenvoudige manier konden prepareren. Uit voorgaand werk was het bekend dat de ethyl ester van (*S*)-melkzuur **1** omgezet kon worden in thioacetaat **2** met volledige inversie van configuratie. Hydrolyse van de ethylester tot het carbonzuur gaf in het verleden onder 'chemische' condities echter altijd aanleiding tot gedeeltelijke racemisatie. Door het gebruik van het enzym PLE (Pig liver esterase), onder neutrale condities, bleek de ethylester selectief gehydrolyseerd te kunnen worden, terwijl het thioacetaat intact bleef. Dit proces verliep zonder racemisatie. Het thioacetaat werd vervolgens met ammonia gehydrolyseerd. Op deze manier kan (*R*)-thiomelkzuur (**3**) in een totaal opbrengst van >65% geprepareerd worden uit het goedkope (*S*)-ethyl lactaat (schema 1).




*Schema 1*

Het (*S*)-thiomelkzuur (**5**) kan gemaakt worden volgens een analoge procedure uit (*R*)-ethyl 2-chloro-propanoaat (**4**). Wij bleken in staat te zijn om deze verbinding in goede opbrengst te maken uit **1** met inversie van configuratie. Ook de analoge stappen verliepen zonder problemen en zodoende waren we in staat om de

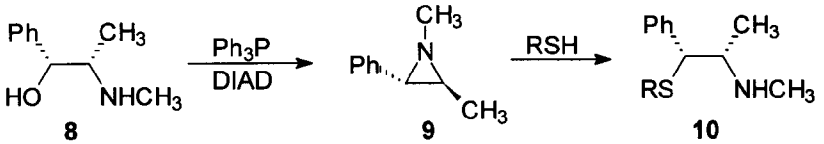
beide enantiomeren van thiomelkzuur in optisch zuivere vorm te produceren, uitgaande van (*S*)-ethyl lactaat (**1**).
In hoofdstuk 2 wordt tevens de synthese beschreven van optisch zuivere thiazolidinonen **6**. Deze verbindingen kunnen gemaakt worden door een condensatie van optisch zuiver thiolmelkzuur (**3**), een amine en een aldehyde. Door deze componenten te variëren is een scala aan chirale verbindingen **6** toegankelijk. Deze thiazolidinonen kunnen gebruikt worden als chiraal ligand in rhodium(I) gekatalyseerde reacties. Tevens kunnen ze omgezet worden in β-amino thiolen **7** via reductie (schema 2). Deze verbindingen **7** zijn succesvol toegepast als chiraal ligand in de asymmetrische additie van diethylzink aan aldehydes (hoofdstuk 4).




**3** **6** **7**

*Schema 2*

β-Amino thiolen zijn interessant aangezien ze een groot potentieel hebben als ligand in de asymmetrische katalyse. In hoofdstuk 3 wordt de synthese beschreven van een ander type β-amino thiolen uitgaande van de alkaloïden efedrine en pseudo-efedrine. Deze optisch zuivere verbindingen komen voor in de natuur en een bekende toepassing van efedrine (**8**) is het gebruik in hoestdrank. Wij hebben **8** echter omgezet in aziridine **9**. Dit chirale aziridine kan selectief geopend worden door een scala aan zwavel nucleofielen waardoor thio analoga **10** van efedrine verkregen worden (schema 3).

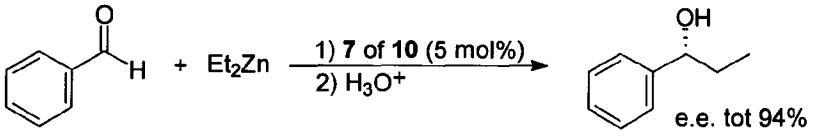



**8** **9** **10**

*Schema 3*

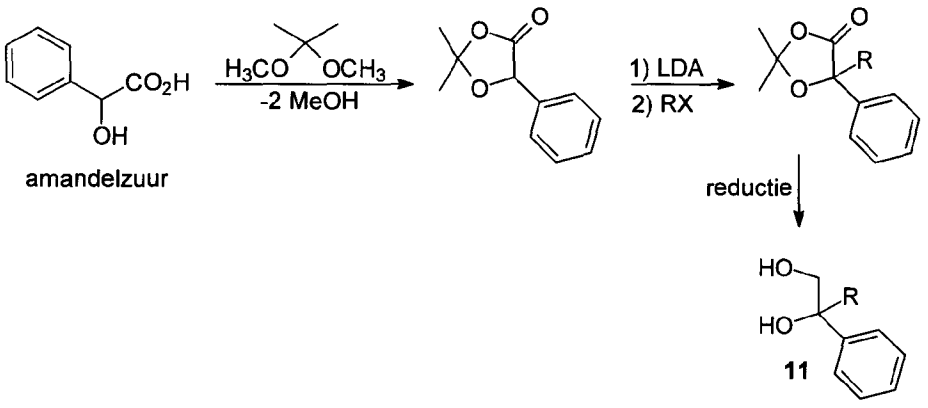
Deze verbindingen blijken uitstekend toegepast te kunnen worden als chirale liganden in asymmetrische katalyse. In hoofdstuk 4 wordt het gebruik van chirale zwavel liganden van de types **7** en **10** in de asymmetrische katalyse beschreven. Als testreactie, om de activiteit van deze nieuwe liganden te onderzoeken, hebben we gekozen voor de additie van diethylzink aan benzaldehyde. Dit is een veel onderzochte reactie, en β-amino alcoholen blijken veelal goede resultaten te geven in deze reactie. Het gebruik van analoge β-amino thiolen is echter nieuw. Verbindingen van type **7** en **10** hebben we

onderzocht in de reactie van schema 4 en het blijkt dat ze veel geschikter zijn dan hun natuurlijk voorkomende zuurstof analoga als **8**.



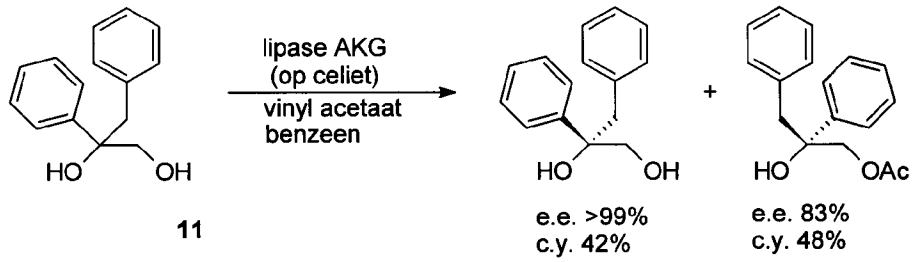

*Schema 4*

De enantiomere samenstelling van het eindproduct wordt doorgaans uitgedrukt in de term e.e. (*enantiomeric excess*). Deze waarde varieert van 0% (racemaat) tot 100% (enantiomeer zuiver product). Waar het natuurlijk voorkomend **8** een e.e. van 60% geeft in deze reactie, geeft zwavel analoog **10** een e.e. van 86%; een duidelijke verbetering. Afhankelijk van het gebruikte aldehyde en ligand kan een maximale e.e. van 94% bereikt worden; een uitstekend resultaat. Ook zijn dit type liganden inmiddels door onze groep, en anderen, toegepast in andere katalytische asymmetrische transformaties.
In hoofdstuk 5 wordt een korte introductie gegeven over het gebruik van enzymen in organische oplosmiddelen aangezien dit een nieuw research onderwerp is in dit laboratorium. In hoofdstuk 6 wordt vervolgens de splitsing van tertiaire diolen **11** beschreven middels lipase gekatalyseerde acylering. Diolen van type **11** zijn interessante bouwstenen voor nieuwe chirale liganden, maar tevens zijn ze door Bayer gebruikt voor de synthese van optisch zuivere fungicides. Allereerst hebben we een algemene synthese methode ontwikkeld, uitgaande van amandelzuur, die verbindingen **11** in goede opbrengsten (70-80%) geeft (schema 5).



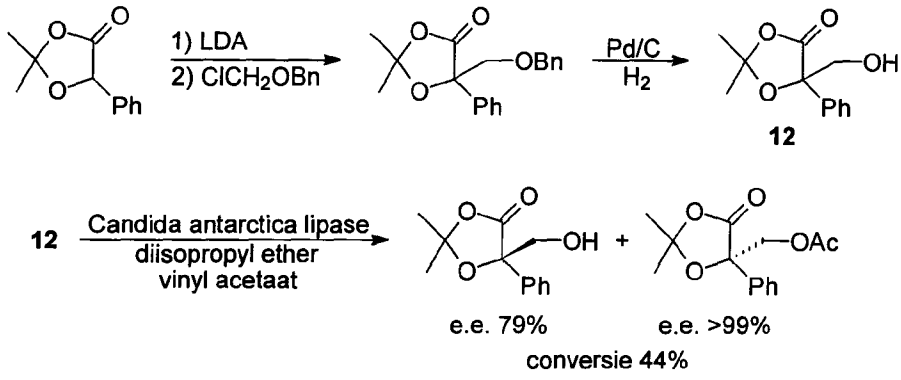

*Schema 5*

Vervolgens hebben we gekeken naar enantioselectieve veresteringen van deze diolen in de aanwezigheid van 16 verschillende lipases. Het bleek dat de meeste lipases wel reactief, maar niet enantioselectief waren voor dit type verbindingen. Een uitzondering bleek lipase AKG, dat met zeer goede chirale herkenning een aantal verbindingen **11** acyleerde. De voorkeur van dit lipase lijkt gebaseerd te zijn op een 'vlakke' alkyl staart op een specifieke positie in het molecule **11**. Door dit unieke verschijnsel waren we in staat een 'active site' model op te stellen voor dit lipase dat kan voorspellen of een verbinding wel of niet enantioselectief omgezet kan worden door lipase AKG. Dit model blijkt in de praktijk uiterst werkbaar te zijn. Tevens hebben we lipase AKG gestabiliseerd door het te absorberen op celiet. Hierdoor kunnen ook op preperatieve schaal (ruim een halve gram) diolen **11** in optisch zuivere vorm verkregen worden (schema 6).




*Schema 6*

In het laatste hoofdstuk (hoofdstuk 7) wordt de resolutie van hydroxymethyldioxolanonen **12** beschreven d.m.v. lipase gekatalyseerde acylering in organische oplosmiddelen. Deze klasse van verbinding met een tertiair chiraal centrum is amper bekend in de literatuur. In de patent literatuur zijn ze eenmalig beschreven als bouwsteen voor fungicides. De daar beschreven synthese route levert echter in slechts lage opbrengst verbindingen **12**. Wij hebben een algemene methode ontwikkeld om verbindingen **12** in goede opbrengst te verkrijgen uit amandelzuur. Tevens blijken we in staat, middels lipase gekatalyseerde acylering, verbindingen **12** te splitsen in de enantiomeren met zeer goede chirale herkenning. In sommige gevallen is absolute chirale herkenning waargenomen, hetgeen inhoud dat uitsluitend één enantiomeer omgezet wordt door het lipase (schema 7).




*Schema 7*

Tevens hebben we initiële pogingen ondernomen om verbindingen **12** om te zetten in tertiaire aryloxypropanolamines. Dit type verbindingen lijkt sterk op bekende $\beta$-blockers als propanolol, een middel dat wordt gebruikt om hoge bloeddruk te bestrijden. Mogelijke toepassingen voor deze verbindingen liggen dan ook in het verschiet.